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FROM THE REVIEWS:

Blood (January 1955): "This is the first volume of what is proposed as an annual series of collective reviews on antibiotics and chemotherapy. As noted in the preface, the articles contain surveys of world literature with detailed bibliographies. They are intended to keep the specialist up to date in his field and also to supply reviews of the latest developments to those not too thoroughly versed in this field.

The international character of this publication is indicated not only by its place of publication in Switzerland, but also by the fact that it has an editor in New York as well as two in Europe.

For those who read fluently in German and French as well as in English, this series deserves a place alongside such well established American series as *Annual Reviews*. It has the advantage of giving somewhat more weight to European literature than is usually found in reviews published in the English language emanating from this country. For those keenly interested in antibiotics it will take its place alongside the journal *Antibiotics and Chemotherapy* and the *Antibiotics Annual* published in this country and will serve as a good supplement to Dr. Welch's *Present Principles of Antibiotic Therapy*."

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A NEW SERUM IODINE COMPONENT IN PATIENTS WITH FUNCTIONAL CARCINOMA OF THE THYROID*†

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CERTAIN carcinomas of the thyroid in man acquire the function of normal thyroid tissue with respect to iodine metabolism (1, 2). Such tumors have the ability to concentrate iodide, convert it to organic form, and secrete organically bound iodine into the blood. They respond to thyrotropic hormone and to goitrogenic drugs with an increased avidity for iodide and, in the absence of normal thyroid tissue, may maintain their hosts in a euthyroid state. Observations on the chemical nature of the iodinated compounds elaborated by these tumors have, however, been scanty. The present report concerns studies on serum radioiodine in 23 patients with functional carcinoma of the thyroid, following 13 tracer doses and 37 therapeutic doses of I^{131}.

Thyroxine, and small amounts of triiodothyronine, constitute essentially all of the circulating iodine in normal and hyperthyroid individuals (3–6).

* *Van Meter Prize Award Essay*, presented at the Annual Meeting of the American Goiter Association, Oklahoma City, Okla., April 28–30, 1955.

This article will be included in the bound volume of the 1955 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available early in 1956.

† This work was supported by a grant from the Damon Runyon Memorial Fund for Cancer Research, a grant from the American Cancer Society, and a contract with the Atomic Energy Commission, No. AT(30-1)-910.

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TABLE 1. CLINICAL AND LABORATORY DATA CORRELATED WITH THE PRESENCE OF ABNORMAL SERUM IODINE COMPONENTS

Patient			Tumor,* histologic pattern	Sites of metastasis	I^{131} Dose		Prior treatment**	Normal thyroid gland	Functional status of thyroid tissue					Abnormal serum I^{131} components§	
Case No.	Sex	Age (yrs.)			Date	mc.			Clinical†	Urine I^{131} (% dose in 48 hrs.)		Whole blood I^{131} (% dose/L at 48 hrs.)		Compound X	Thyroglobulin
										Tracer‡	Therapy	Tracer‡	Therapy		
1	M	24	papillary and follicular	neck, lung	July 1952	246	Total TX, Mar. 1952	Absent	Hypothyroid	39	47	1.08	1.42	++	0
					Feb. 1953	0.46	Thiouracil	Absent	Hypothyroid	47		0.66		++	0
					Mar. 1953	302	Thiouracil	Absent	Hypothyroid		72		0.63	++	0
2	F	49	solid	neck, lung	Dec. 1951	1	Partial TX, 1947	Partially intact	Hyperthyroid	44				++	0
					Dec. 1951	198		Partially intact	Hyperthyroid		63		0.76	++	0
3	F	15	papillary, alveolar, and follicular	neck, lung	Mar. 1951	2	Partial TX, 1947 I^{131}, 75 mc., 262 mc., 1948 Thiouracil	Absent	Hypothyroid	35				?	?
					Mar. 1951	107	Thiouracil	Absent	Hypothyroid		65		1.00	+	?
					June 1952	153	Tapazole	Absent	Hypothyroid	62	76		0.42	+	0
					Dec. 1953	1	Tapazole	Absent	Hypothyroid					+	0
					Dec. 1953	241	Tapazole	Absent	Hypothyroid					++	0
4	F	32	papillary and follicular	neck, lung, kidney	Nov. 1952	63	Partial TX, 1943	Partially intact	Euthyroid	46	57			+	++
					June 1953	0.50	Thiouracil	Absent	Hypothyroid?	12		0.38		0	0
					June 1953	177	Thiouracil	Absent	Hypothyroid?		16		0.37	++	0
5	F	78	solid and follicular	neck, mediastinum, bone	Feb. 1952	0.46	Partial TX, 1940 X-ray Rx to bone, 1948	Partially intact	Euthyroid	74		0.58		?	0
					Feb. 1953	356		Partially intact	Euthyroid		50		0.65	++	++
					May 1953	0.31		Absent	Euthyroid	77		0.31		?	0
6	M	50	trabecular	neck, trachea, lung	Apr. 1953	295	Total(?) TX, 1950 Propylthiouracil	Absent?	Euthyroid	49	66	0.35	1.17	++	++
7	F	13	papillary and follicular	neck, lung	Jan. 1954	293	Total(?) TX, 1949 I^{131}, 76 mc., Apr. 1953 Tapazole	Absent	Hypothyroid	60	20		0.62	++	0
8	F	34	papillary	neck, mediastinum	Mar. 1954	155	Total TX, July 1953 Tapazole	Absent	Hypothyroid?	60	70		0.64	+	?
9	F	60	alveolar and follicular	neck, lung	Jan. 1951	254	Partial TX, 1926 and 1945	Partially intact	Hyperthyroid	42	31	1.22	1.98	+	?
10	F	69	papillary	lung, bone	Apr. 1952	207	Partial TX, 1945 X-ray Rx to bone, 1948 I^{131}, 200 mc., Dec. 1951	Absent	Euthyroid	37		0.50		+	++
					Sept. 1953	0.47		Absent	Euthyroid	29		0.48		?	0
					Oct. 1953	150		Absent	Euthyroid		52		0.46	+	++
11	F	77	follicular	neck, skull	Sept. 1951	247	Thiouracil	Intact	Euthyroid		12			0	?
					Apr. 1952	176	Thiouracil	Absent	Hypothyroid	21	42			+	++
12	F	58	alveolar and follicular	neck, lung, bone	Sept. 1952	241	I^{131}, 75 mc., June 1952	Absent	Euthyroid		31		0.31	+	++
					Feb. 1953	263		Absent	Euthyroid	48				0	++
13	F	56	follicular	neck, lung, bone	Mar. 1953	174	Total TX, 1952 X-ray Rx to neck, 1949 X-ray Rx to bone, 1952 Thiouracil	Absent	Euthyroid	36	72	2.02	1.29	0	?
					Dec. 1953	251	Tapazole	Absent	Euthyroid	24	53	1.57	0.79	+	0

					Dec. 1953	251	Thiouracil Tapazole	Absent	Euthyroid	24	53	1.57	0.79	+	0

Patient			Tumor,* histologic pattern	Sites of metastasis	I^{131} Dose		Prior treatment**	Normal thyroid gland	Functional status of thyroid tissue					Abnormal serum I^{131} components‡	
									Clinical†	Urine I^{131} (% dose in 48 hrs.)		Whole blood I^{131} (% dose/L at 48 hrs.)			
Case No.	Sex	Age			Date	mc.				Tracer‡	Therapy	Tracer‡	Therapy	Compound X	Thyroglobulin
14	F	26	papillary	neck, lung	Mar. 1953	75	Partial TX, 1941 and 1943	Partially intact	Euthyroid	50	56		0.20	++	0
					Oct. 1953	0.51	Tapazole	Absent	Hypothyroid	24		0.38		−−¶	−−¶
					Oct. 1953	249	Tapazole	Absent	Hypothyroid		30		0.95	−−¶	−−¶
15	M	17	follicular	neck, lung	Mar. 1951	2	I^{131}, 25 mc., 1947; 112 mc., 1948; thiouracil	Absent	Hypothyroid	18				0	0
					Mar. 1951	107	Thiouracil	Absent	Hypothyroid		20			?	?
					Aug. 1952	123		Absent	Hypothyroid	38	50		1.96	0	?
16	F	55	solid and follicular	neck, lung, liver	Sept. 1951	0.74	Partial TX, 1949 X-ray Rx to neck, 1949	Partially intact	Euthyroid	23		0.45		0	0
					Oct. 1951	200		Partially intact	Euthyroid		29			?	?
17	F	16	papillary and alveolar	lung	Oct. 1951	235	Partial TX, 1947 I^{131}, 75 mc., 1948; 25 mc., 1949	Absent	Hypothyroid?					?	?
18	F	35	follicular	neck, lung	Feb. 1951	51	Partial TX, 1945, 1946, 1949 X-ray Rx to neck, 1948	Partially intact	Euthyroid	50	52		0.29	0	?
19	F	32	solid and follicular	lung, liver, bone	Sept. 1951	150	Partial TX, 1936, 1943 Total TX, 1948 I^{131}, 30 mc., 1950 Tapazole	Absent	Hypothyroid?	51	60	0.33	0.37	0	?
20	F	56	Hürthle-cell and follicular	bone	May 1951	0.82	Total TX, 1950 I^{131}, 50 mc., 53 mc., 200 mc., 1950; 225 mc., Jan. 1951	Absent	Hypothyroid	8				0	0
					May 1951	182		Absent	Hypothyroid		27		2.00	0	?
					Mar. 1952	169		Absent	Hypothyroid	24	17		1.04	0	0
					Feb. 1953	155	Thiouracil	Absent	Hypothyroid	33	36		0.77	0	?
21	F	43	alveolar	bone	Aug. 1951	79	Partial TX, 1943 I^{131}, 33 mc., 231 mc., 60 mc., 91 mc., 160 mc., 1947; 200 mc., 1948; 100 mc., 1950 Thiouracil	Absent	Hypothyroid?					0	0
					Oct. 1953	153		Absent	Hypothyroid?					0	0
22	F	54	alveolar and follicular	neck, lung, bone	Sept. 1952	1	Total TX, Aug. 1952 X-ray Rx to bone, Aug. 1952	Absent	Euthyroid	43		1.04		0	0
					Oct. 1952	200		Absent	Euthyroid		47		1.63	0	0
					Apr. 1953	174	Thiouracil	Absent	Euthyroid	5	14	1.47	2.34	0	0
23	M	73	solid	larynx, trachea, mediastinum	Aug. 1953	238	Partial TX, 1952 I^{131}, 67 mc., Jan. 1953 Tapazole	Absent	Hypothyroid	67	69		0.56	0	0

* Small biopsy specimens in some cases. It is probable that all cases had follicular or alveolar elements.
** TX indicates thyroidectomy.
† Based on cholesterol, BMR and PBI values, and clinical evaluation.
‡ Results following I^{131} tracer given one month or less before the therapy dose.
§ ++ =present; + =probably present; ? =indeterminate; 0 =absent.
¶ Indeterminate, due to the presence of gamma globulin-bound thyroxine. The findings in this patient will be described in detail elsewhere.

These compounds have also been demonstrated in serum from patients with functional carcinoma of the thyorid, even in the absence of normal thyroid tissue (7–9). Thyroglobulin which has been discharged into the blood from intensively irradiated thyroid carcinoma likewise resembles normal thyroglobulin (8–11). Investigations employing zone electrophoresis have revealed a specific thyroxine-binding protein in serum from patients with thyroid carcinoma, which is similar to that in normal or hyperthyroid subjects (11–16). In the present study, however, a new serum iodine component has been found. The characteristics of this abnormality will be described, and its nature discussed.

MATERIALS AND METHODS

The patients are listed in Table 1, together with certain clinical and laboratory data. Included are all cases of carcinoma of the thyroid treated with radioiodine[1] at the Memorial Center, New York City, and most of those treated at the hospital of the Brookhaven National Laboratory, Upton, New York, during a period of three and one-half years. The sole basis for selection, other than inoperability, was the presence of a considerable uptake of I^{131} by the tumor. In the majority, a high avidity for iodide was induced by thyroidectomy, or thiouracil administration, or both (see Table 1).

Serum,[2] obtained at intervals varying from one hour to twenty-eight days after the radioiodine doses, was subjected to two or more of the following analytical procedures: [i] extraction with *n*-butanol, employing either untreated serum (8), or serum acidified with trichloroacetic acid (17); [ii] precipitation of total serum protein with zinc hydroxide (18); [iii] salting out of serum protein with increasing concentrations of potassium phosphate buffer (9); [iv] paper chromatography of whole serum, or of the butanol extract of serum (8, 11), in one or more of the following solvent systems: a) *n*-butanol-2,4-dioxane-ammonia (19), b) *n*-butanol-primary amyl alcohol-ammonia (11), c) *n*-butanol-acetic acid-water (5); [v] zone electrophoresis in barbital buffer, pH 8.6 (11, 20). Details of these procedures are given in the references. Additional procedures employed will be described under Results.

Radioiodine in liquid samples was measured in a well-type Geiger-Mueller or scintillation counter. Radioactivity on paper strips was measured with a thin mica-window Geiger-Mueller tube, either by sectioning the strips and counting the segments (8) or by means of a continuously recording counting-rate meter (20).

[1] Radioiodide (I^{131}) was obtained from Oak Ridge, Tennessee, and administered with less than 10 micrograms of carrier iodide.

[2] In Case 21, heparinized plasma was used.

RESULTS

Variations in the numbers and types of procedures which were performed on each of the sera, as well as a considerable variability in the proportions of the several serum iodine components (*see* subsequent data), preclude a concise and inclusive presentation of the findings. Consequently, illustrative examples will be presented, followed by an evaluation of the data with

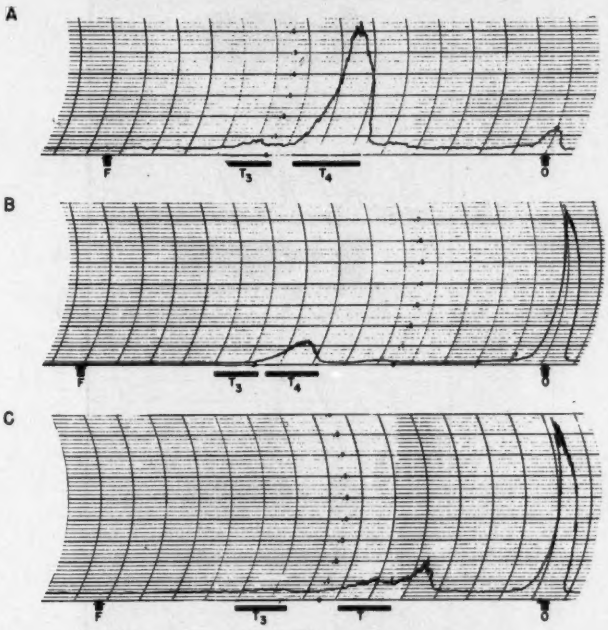

FIG. 1. *Paper chromatograms of whole serum in the butanol-dioxane-ammonia system.* **A.** Case 22 (Apr. 1953) one day after 174 mc of I^{131}; **B.** Case 6, four days after 295 mc; **C.** Case 1 (Mar. 1953) four days after 302 mc. The tracings represent radioactivity on the paper strips. O = origin, F = solvent front, T_4 = carrier thyroxine, T_3 = carrier triiodothyronine. The radioiodine peak with an R_f just below T_4 coincides with that of iodide. The major peaks in the graphs are: **A.** thyroxine; **B.** thyroglobulin; **C.** compound X.

respect to the presence or absence of these several components in the sera. Representative serum radioiodine analyses are presented in Figures 1 to 4. Sera in which thyroxine or thyroglobulin constituted the major portion of the serum I^{131} are compared with serum which contained a large radioiodine component different from either of these. This material will be designated compound X, although the possibility exists that it may not be a single substance.

The chromatographic analyses of whole serum in Figure 1 are characteristic of the findings in the three solvent systems. Compound X remained at the origin in all and, in this respect, did not differ from thyroglobulin. Figure 1A also demonstrates the presence of triiodothyronine,

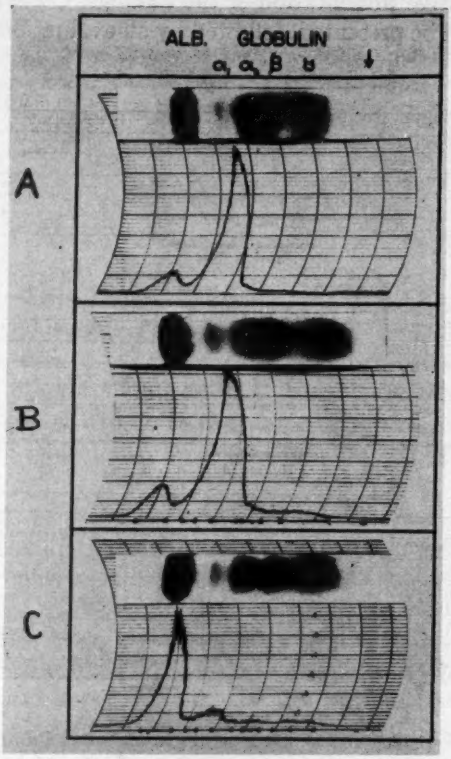

FIG. 2. *Zone electrophoresis of serum at pH 8.6.* **A.** Case 22 (Apr. 1953) four days after 174 mc of I^{131}; **B.** Case 6, four days after 295 mc; **C.** Case 1 (Mar. 1953) four days after 302 mc. The paper strips, stained with bromphenol blue, are aligned with records of their radioactivity contents. The arrow indicates the point of application. The major radioiodine components are: **A.** thyroxine, **B.** thyroglobulin, **C.** compound X.

which was detected in sera from 9 of 15 patients in whom butanol-dioxane-ammonia chromatograms were obtained.[3]

Although the electrophoretic analyses at pH 8.6 (Fig. 2) did not differ-

[3] Triiodothyronine, when present, constituted from 1 to 7 per cent of serum organic I^{131}. In 9 patients, chromatograms contained from 1 to 10 per cent of serum I^{131} in other components of uncertain identity. In 6 of these patients this material may have been monoiodotyrosine or diiodotyrosine.

entiate between thyroxine and thyroglobulin in serum, each having a mobility between alpha-1 and alpha-2 globulin (11, 21), the major radioiodine peak in the serum containing compound X was found in the albumin area. The peak for compound X also coincided with the major albumin peak in electrophoretic analysis at pH 4.5 (20). Further similarities between compound X and serum albumin are demonstrated in Figures 3

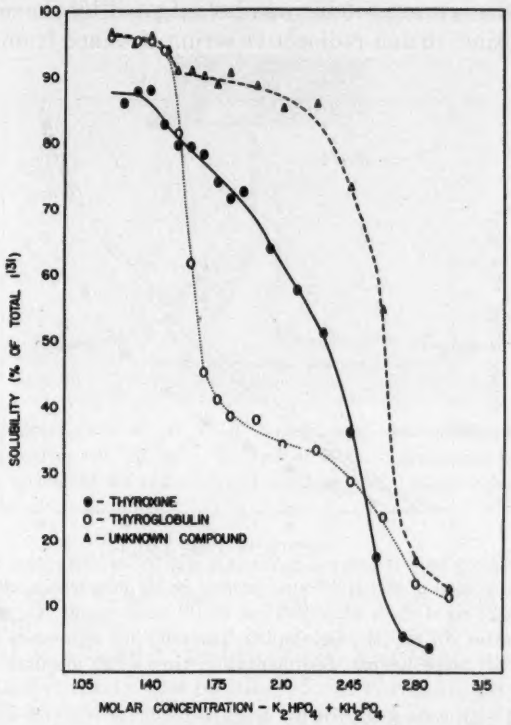

FIG. 3. *Salting-out of serum I^{131} with phosphate buffer, pH 6.5:* ● = Case 20 (Feb. 1953) six days after 155 mc of I^{131}; ○ = Case 12 (Sept. 1952) eight days after 241 mc; Δ = Case 1 (July 1952) four days after 246 mc.

and 4. Compound X was more soluble in phosphate buffer than either serum thyroxine or thyroglobulin (9) and had a salting-out curve indistinguishable from that of purified human serum albumin.[4] In the preparative ultracentrifuge, compound X had a sedimentation rate close to that of

[4] Obtained through the courtesy of Dr. S. T. Gibson of the American Red Cross, and Dr. J. N. Ashworth of E. R. Squibb and Sons.

the average serum protein and differed from thyroglobulin, which had a much faster rate. In the partition cell, the sedimentation constant was found to be approximately 4.2 S, which is like that of serum albumin and somewhat faster than that of the thyroxine-binding protein (22). (Ultracentrifugal analysis[5] was performed on 3 sera—Case 1, July 1952 and March 1953; Case 4, June 1953—by techniques described earlier (10, 22).)

The possibility that compound X might represent abnormal binding of thyroxine by the serum proteins was investigated by the addition of I^{131}-labeled *l*-thyroxine[6] to non-radioactive serum obtained from the patient in

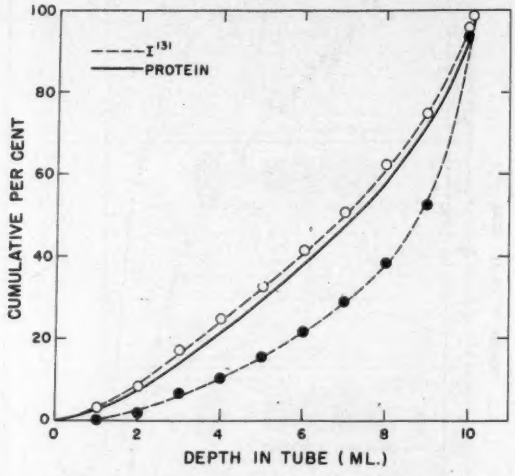

FIG. 4. *Sedimentation of serum I^{131} and protein in the preparative ultracentrifuge.* ○ = Case 1 (July 1952) eight days after 246 mc of I^{131} (compound X); ● = Case 10 (Apr. 1952) nine days after 207 mc (thyroglobulin). The solid line represents mean total serum protein for the two experiments. Sedimentation time = 120 minutes at 152,000 times gravity.

Case 1 prior to the second therapy dose. The distribution of thyroxine-I^{131} among the protein fractions (Fig. 5) was similar to that observed with normal serum at comparable thyroxine concentration (11).

Compound X was wholly precipitated from serum by 2.98 M phosphate buffer, by zinc hydroxide, and by 5 per cent trichloroacetic acid, and it could not be removed from the serum (Case 1) by dialysis in Visking tub-

[5] The authors are indebted to Dr. M. L. Petermann of the Sloan-Kettering Institute, for these determinations.

[6] L-thyroxine-I^{131} was obtained from Abbott Laboratories, Oak Ridge, Tennessee. The preparation used in these experiments had a purity of 72 per cent on chromatographic analysis.

ing against running tap water for seventy-two hours. Repeated extractions of serum (Case 1) with *n*-butanol at neutral or alkaline pH removed little or no compound X, but when the serum was first acidified with trichloroacetic acid, the butanol extract contained from 25 to 45 per cent of the I^{131} which was present in this abnormal form. By appropriate corrections for thyroxine-^{131} and iodide-I^{131} in other sera which contained compound X, a similar solubility in acid butanol was found. Thyroglobulin, on the other hand, was much less soluble in butanol under these conditions. Re-

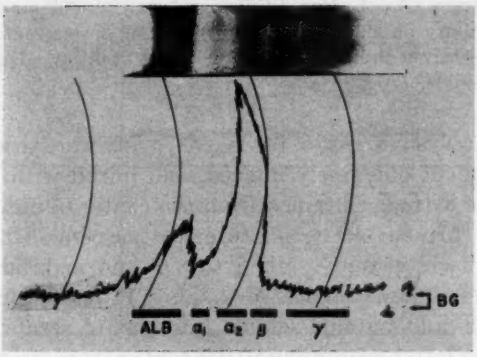

FIG. 5. *Zone electrophoresis at pH 8.6 of a mixture of non-radioactive serum (Case 1) and* I^{131}*-labeled l-thyroxine (.02 μg./ml.).* The paper strip, stained with bromphenol blue, is aligned with a record of its radioactivity content. BG indicates background radioactivity.

peated butanol extractions of the acidified serum (Case 1), with or without the addition of more trichloroacetic acid, failed to remove any of the orginally insoluble residue.

Evidence that compound X, or some fraction of compound X, was present in the butanol extracts was obtained from chromatographic analyses. As illustrated in Figure 6, the butanol solutions contained I^{131} which was immobile on the chromatograms. It was of further interest that the extracted abnormal material was largely nondialyzable. Employing the same procedure as previously described for whole serum, 81 per cent of the radioiodine present in abnormal form in the butanol extract of serum (Case 1) remained in the dialysis bag. Thyroxine, on the other hand, was entirely dialyzable under these conditions.

It consequently became of interest to determine whether smaller iodine-containing fragments might be liberated from compound X by hydrolysis. Five sera which appeared to be free of thyroglobulin were selected (Table 2). Compound X in 0.5 or 1 ml. of serum was separated from thyroxine, triiodothyronine, and iodide by chromatography in the butanol-amyl

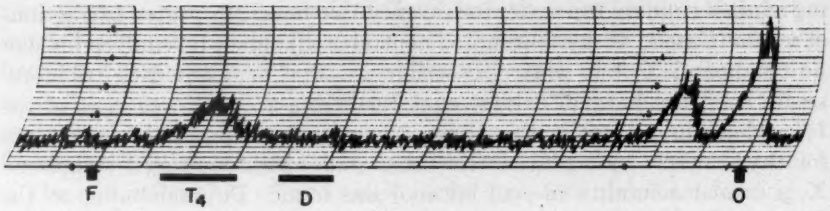

FIG. 6. *Paper chromatogram in the butanol-acetic acid system of the trichloroacetic acid-butanol extract of serum.* Case 1 (Mar. 1953) four days after 302 mc of I^{131}. The tracing represents radioactivity on the paper strip. O = origin, F = solvent front, D = carrier diiodotyrosine, T_4 = carrier thyroxine. The radioiodine peak just above the origin coincides with that of iodide.

alcohol-ammonia system. After the paper strips were dried, the areas of application were cut out, finely minced, and mixed with 10 or 20 mg. of crude pancreatic extract, obtained from the center of enteric-coated pancreatin tablets (Armour). The mixture was suspended in 2 to 5 ml. of bicarbonate or barbital buffer, pH 8 to 8.6, and maintained at 37.5° C. for seventy-two hours with repeated shaking. In one serum (Table 2), the butanol-insoluble and butanol-soluble fractions of serum were subjected to hydrolysis, the latter containing 80 per cent of its radioiodine in the form of compound X. In 3 instances (Table 2), hydrolysis with barium hydroxide was performed by a modification of the method of Blau (23), and the barium then removed by acidification with sulfuric acid.

TABLE 2. HYDROLYSIS OF COMPOUND X

Case	Date of I^{131} dose	Time after dose	Starting material	Hydrolysis method	Results of chromatographic analysis* (% of I^{131} in hydrolysate)			
					Monoiodotyrosine	Diiodotyrosine	Thyroxine	Immobile material
1	July 1952	8 days	BuOH-insoluble	Barium hydroxide	55	0(?)	0	9
	July 1952	8 days	BuOH-soluble	Barium hydroxide	70	0(?)	1	5
	Mar. 1953	4 days	Chromatogram origin	Barium hydroxide	55	4	0	18
	Mar. 1953	4 days	Chromatogram origin	Enzymatic	53	2	7	23
3	Dec. 1953	18 hrs.	Chromatogram origin	Enzymatic	54	6	3	9
4	June 1953	7 hrs.	Chromatogram origin	Enzymatic	8	3	71	4
7	Jan. 1954	4 days	Chromatogram origin	Enzymatic	54	6	2	15

* The values are based on analyses in the butanol-acetic acid system. The other solvent systems yielded comparable, but not always identical, results. The presence of small amounts of diiodotyrosine and thyroxine was not always certain, even when numerical values are recorded. In Case 1 (Mar. 1953), 7 per cent of the I^{131} in the alkaline hydrolysate and 9 per cent in the enzymatic hydrolysate had the solubility characteristic of thyroxine (*i.e.*, extractable with *n*-butanol, and not removed from the butanol extract by strong alkaline washing).

The supernatant fluid from each of the hydrolysis mixtures was subjected to chromatographic analysis in the butanol-acetic acid system and in one or both of the alkaline butanol systems, and runs were made with and without carrier thyroxine, triiodothyronine, diiodotyrosine, and monoiodotyrosine. In the alkaline butanol solvent systems, it was found that more satisfactory chromatographic separations could be obtained when the hydrolysate was first adjusted to pH 3. Representative analyses of the hydrolysate in Case 1 (Mar. 1953) are presented in Figure 7. The major

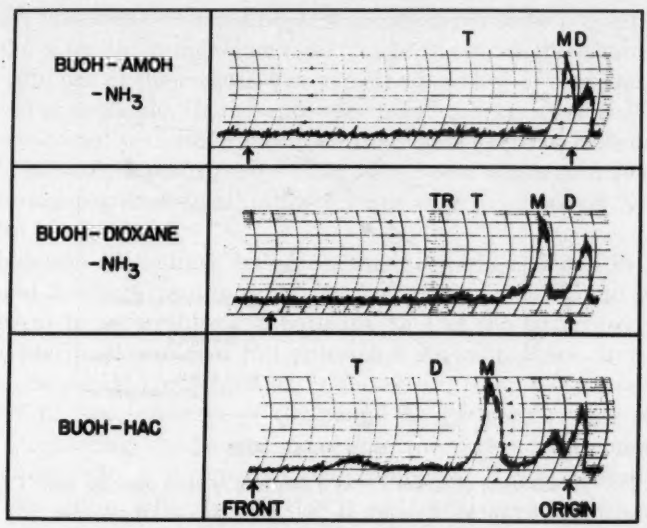

FIG. 7. *Paper chromatograms of the enzymatic hydrolysate of compound X.* Case 1 (Mar. 1953) four days after 302 mc of I^{131}. The headings indicate the chromatographic systems, and the tracings represent radioactivity on the paper strips. Carrier substances are: D = diiodotyrosine, M = monoiodotyrosine, T = thyroxine, TR = triiodothyronine. In the alkaline-butanol systems, acidification of the hydrolysate prior to chromatography probably accounts for the lower thyroxine peak, since a small precipitate formed and was discarded.

radioiodine peak, which contained about 50 per cent of the total I^{131} in the hydrolysate, coincided with that of carrier monoiodotyrosine in each of the chromatographic systems. About 25 per cent remained immobile, and may have represented incompletely hydrolyzed compound X. A small amount of the radioiodine was found in the thyroxine region, and very little accompanied the diiodotyrosine carrier. As many as 3 other radioiodine components of unknown nature were detected in the various chromatographic analyses, but are not all illustrated in Figure 7.

The data in Table 2 indicate similar findings in 2 other patients. In a third patient, however, the major radioiodine peak in the hydrolysate appeared to be thyroxine, and constituted about 70 per cent of the total I^{131}.

It is clear from the foregoing experiments that the characteristics of compound X resemble, in certain respects, those of thyroxine and thyroglobulin. Although the presence of compound X was unmistakable in instances such as that illustrated in Figures 1 to 4, in which a major portion

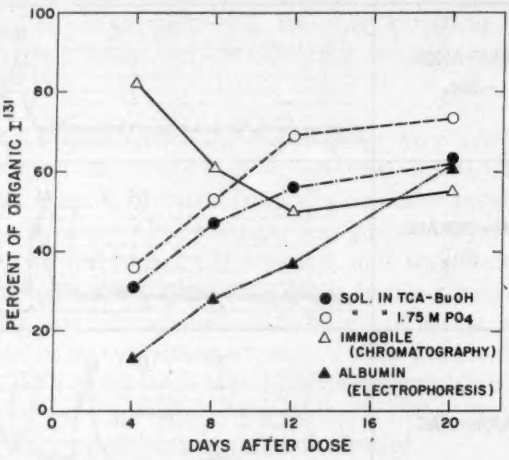

FIG. 8. *The characteristic of serum I^{131} as a function of time after the dose.* Case 6. The major radioiodine component in serum at four days was thyroglobulin, but serum at twenty days contained a large I^{131} component characteristic of compound X. Chromatography of the TCA-butanol extract of the four-day serum revealed that 22 per cent of the butanol-soluble I^{131} was immobile.

of the total serum I^{131} was in this abnormal form, the admixture of other serum iodine components in large amounts made the detection of compound X more difficult. An illustration of one such situation is presented in Figure 8 (Case 6). In this instance, compound X was obscured by the presence of large amounts of thyroglobulin. Only in serum obtained later than twelve days after the radioiodine dose, when thyroglobulin had decreased, was the presence of compound X clearly discernible. The sum of the I^{131} soluble in 1.75 M phosphate buffer plus that immobile on chromatography, however, was always between 114 and 126 per cent. This indicates the presence of material which is both soluble in the buffer and immobile in the chromatograms. It is possible that thyroglobulin, in very low concentration, may be soluble to some degree in 1.75M phosphate (9),

but it is perhaps more likely that this sum in excess of 100 per cent is due to the presence of compound X, even in the four-day serum.

The following criteria were established to define the presence of compound X in serum: 1) more than 30 per cent of organic I^{131} in the albumin area in electrophoresis, 2) more than 100 per cent of organic I^{131} in the combined origin area in chromatograms of whole serum plus soluble fraction in 1.75M phosphate, and 3) more than 15 per cent of organic I^{131} in the origin area in chromatograms of the butanol extract of serum. Only sera containing less than 50 per cent of the total I^{131} as iodide were used for these evaluations. Compound X was considered to be present when, at some time after the radioiodine dose,[7] at least two of these criteria were met. If only one of the criteria was met, the presence of compound X was considered as probable. Its presence was indeterminate when the foregoing analyses were not performed but more than 30 per cent of organic I^{131} was insoluble in butanol and/or more than 15 per cent was immobile on whole serum chromatograms. In all other circumstances, compound X was considered to be absent.

A tabulation of findings based on these criteria is given in Table 1. Compound X was present in sera from 8 of the 23 patients, and was probably present in an additional 6 patients. In 4 of the latter group (Cases 10–13), criterion 2 was met, but criterion 1 was not. Since thyroglobulin (*see* next paragraph) was present in the serum from 3 of these patients (Cases 10–12), the presence of compound X was perhaps less certain in these. Disregarding the patients in whom the presence of compound X was indeterminate, it is apparent that compound X was present in from 40 to 70 per cent of patients, and that it was found on more than one occasion in several patients. These results will be considered further under Discussion.

Thyroglobulin (Table 1) was considered to be present in serum when less than 57 per cent of organic I^{131} was soluble in 1.75M phosphate buffer (*i.e.*, more than twice the standard deviation below the mean solubility of serum thyroxine (9)). Its presence was indeterminate when salting-out was not performed, but more than 30 per cent of organic I^{131} was insoluble in butanol and/or more than 15 per cent was immobile in whole serum chromatograms. Otherwise, thyroglobulin was considered to be absent.

Thyroxine was detected in all sera subjected to chromatographic analysis, regardless of the presence or absence of normal thyroid tissue in the patient. Normal thyroid tissue was absent in all 9 patients in whom triiodothyronine was detected.

[7] In most patients in whom compound X was present, it was detected in multiple serum samples, from as early as seven hours to twenty-eight days following the radioiodine doses.

DISCUSSION

The results recorded in Table 1 indicate that compound X is a not uncommon constituent of the serum iodine in patients with highly functional carcinoma of the thyroid. Indeed, it may well be present in more than two thirds of such patients. Although compound X apparently had not been detected in most electrophoretic studies on serum radioiodine in patients with thyroid carcinoma (12–14, 16), Horst and Rösler (15) reported a very large albumin-I^{131} component in 1 of 3 such patients. Column chromatographic studies on acid-butanol extracts of serum (7) could have failed to demonstrate the presence of compound X if this substance had remained on the column.

A review of reports dealing with the nature of serum radioiodine in normal and hyperthyroid human subjects (5–9, 11–13, 15, 16, 20, 22, 24–26), as well as unpublished data on such subjects from our laboratory, has failed to reveal findings comparable to those in the present study. The significance of the observation by Larson *et al.* (26) that albumin-I^{131} could not be extracted with butanol following electrophoresis of hyperthyroid serum on starch, is not clear, inasmuch as serum which contains I^{131} only in the form of thyroxine presents a similar albumin-I^{131} component (11).

Although many of the characteristics of compound X resemble those of serum albumin, the results of trichloroacetic acid-butanol extraction indicate that compound X is probably not an integral part of the albumin molecule.[8] Thus compound X does not appear to result from iodination of serum albumin in the nonspecific manner common to many proteins *in vitro* (27). The failure to find this abnormal compound following radioiodine therapy in patients without thyroid carcinoma is also against this possibility. This difference is not related to the size (in millicuries) of the radioiodine doses, since compound X has been detected after a dose as small as 0.46 millicurie. It is uncertain whether or not compound X is in actual combination with albumin in serum, but the data indicate that compound X itself is a large molecule.

The products of hydrolysis of compound X are unlike those which would be expected if compound X were a fragment of normally synthesized thyroglobulin (8). In studies on rats (28, 29), diiodotyrosine was the major radioiodine component in thyroid gland hydrolysate, and a considerable amount of radiothyroxine was present, as early as ten minutes after radioiodide injection. In the absence of specific-activity data on the

[8] Since this manuscript was submitted, control experiments employing iodinated human serum albumin (Abbott) added to normal serum have indicated that this material behaves in a manner similar to compound X with regard to TCA-butanol extraction.

hydrolytic products of compound X, however, the possibility of the secretion of thyroglobulin fragments very early in the course of iodine incorporation cannot be dismissed. This argument would not pertain to Case 4, in which hydrolysis of compound X released mainly thyroxine.

Although direct evidence is lacking, it is probable that compound X is a product of the functional carcinoma. It appears to result from a defect in thyroid hormone synthesis, although a defect in proteolysis and secretion might be a factor in some instances. Since compound X has been found in serum after small doses of I^{131}, these defects are probably unrelated to the effects of irradiation, but are rather due to abnormal iodine metabolism in the thyroid tumor per se. It will be of interest to learn whether this abnormality is specific for thyroid carcinoma or whether it may be induced by other thyroid neoplasms.

Analysis of the data presented in Table 1 provides no clinical or laboratory features which are uniquely common to those patients in whom compound X was found. It is noteworthy, however, that compound X, as well as thyroxine, triiodothyronine, and thyroglobulin, has been found in serum from patients whose normal thyroid tissue was totally ablated.

SUMMARY AND CONCLUSIONS

The nature of the serum iodine has been examined in 23 patients with highly functional carcinoma of the thyroid, after 13 "tracer" doses and 37 "therapeutic" doses of I^{131}. Although these tumors appear to be capable of synthesizing normal thyroglobulin and secreting thyroxine and triiodothyronine into the blood, more than half of the patients studied were found to have in addition a serum iodine component different from the products of normal thyroid metabolism. This substance (compound X), which may not be a homogeneous material, is in the form of a large molecule and appears to be secreted by the tumor. Compound X is partly soluble in acid butanol, immobile in various chromatographic systems which employ butanol, and resembles serum albumin in several respects. It can be hydrolyzed by crude pancreatic enzymes, with the release of a high proportion of monoiodotyrosine in some instances, and thyroxine in another.

Compound X appears to represent a functional abnormality in certain thyroid carcinomas. No correlation has been thus far detected between various clinical and laboratory features of these patients and the abnormal serum iodine findings.

Acknowledgments

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MALIGNANT LYMPHOMA OF THE THYROID GLAND AND ITS RELATION TO HASHIMOTO DISEASE: A CLINICAL AND PATHOLOGIC STUDY OF 8 PATIENTS*†

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MALIGNANT lymphoma (lymphosarcoma) is an uncommon, primary neoplasm of the thyroid gland. Unlike most epithelial thyroid neoplasms, malignant lymphoma is usually characterized by a rapidly fatal course. The majority of the recorded cases of malignant lymphoma of the thyroid gland, including lymphosarcoma and reticulosarcoma, have been reviewed and tabulated by Dinsmore *et al.* (1), Kellett and Sutherland (2), and Brewer and Orr (3). Most of the patients reported were elderly women with rapidly growing goiters of recent origin, commonly associated with local symptoms of pressure. Usually the patients survived for only seven months to two years following surgical or radiation therapy.

The present study concerns 8 patients with malignant lymphoma originating in the thyroid gland. The glands of 7 of the 8 patients also displayed the characteristic lesions of Hashimoto disease. The relationship between these two thyroid processes appears significant.

The purposes of this report are 1) to describe the clinical manifestations of malignant lymphoma in these 8 patients and the course and results of surgical and radiation therapy, 2) to describe and illustrate the pathologic features of the disease, and 3) to discuss the relationship between malignant lymphoma and Hashimoto disease occurring together in the thyroid gland.

CASE REPORTS

Case 1

A 73-year-old white man had noted a firm swelling in the thyroid region for one month. The thyroid gland was symmetrically enlarged and firm. The white blood cell

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count and differential count were normal. The clinical diagnosis was colloid goiter, and subtotal thyroidectomy was performed. The gland was densely adherent to adjacent structures, and many cervical lymph nodes were enlarged. Roentgen examination of the chest following thyroidectomy showed no mediastinal masses. For three weeks following operation external irradiation with x-rays (1,800 r in air) was delivered to both sides of the neck through wide ports. Soon after completion of the radiation therapy, the patient manifested progressive dysphagia with frequent aspiration of ingested fluids. Shortly before death a pharyngeal mass and rectus paralysis of the right eye appeared. Death occurred ten months after the onset of thyroid enlargement. An autopsy revealed bilateral bronchopneumonia with multiple pulmonary abscesses resulting from aspiration of food. No neoplastic tissue was found within the neck or in the thoracic, abdominal, or cranial cavities.

The thyroid tissue (S52-885) removed surgically was pale, greyish-white, firm, and rubbery and contained small circumscribed necrotic zones.

Almost the entire thyroid glandular parenchyma and capsule were replaced by neoplastic tissue consisting of a variety of pleomorphic neoplastic cells which had produced a diffuse collagenous and reticulum stroma. The predominant cells were lymphoid and included stem cells, lymphoblasts, and mature lymphocytes. There were many scattered large bizarre cells characterized by extreme pleomorphism and generally by nuclear hyperchromatism (Fig. 1). Some of these cells had one or more vesicular nuclei containing prominent eosinophilic nucleoli and a coarse chromatin network. The cytoplasm was irregularly outlined, abundant and eosinophilic. Numerous mitotic figures were observed throughout the neoplasm and were more often found in the large multinucleated cells.

Numerous zones of necrosis, often surrounded by palisading fibroblasts and reticuloendothelial cells, were observed. Some necrotic zones appeared infarcted and retained the faint outlines of their previous structure. In others, the necrotic tissue was amorphous and granular. Many arteries displayed narrowed lumens due to infiltration of their layers by neoplastic cells or intimal fibrous thickening.

A diffuse, delicate reticulum network was intimately associated with the neoplastic cells. In some portions of the gland there were residual thyroid epithelial cells forming follicles. Some contained colloid, others were filled with desquamated cells, and a few contained syncytial multinucleated groups of epithelial cells.

One segment of the thyroid gland showed no neoplastic involvement but displayed the pattern of Hashimoto disease (Fig. 2). The thyroid epithelium generally was arranged in small groups of cells often without follicular formation. These epithelial cells were moderately pleomorphic and contained pleomorphic nuclei and abundant homogeneous eosinophilic cytoplasm. Interlobular fibrosis and infiltration with mature lymphocytes were observed about these areas.

Case 2

A 21-year-old white man had stiffness of the neck for one month, followed by progressive swelling of the lower anterior aspect of the neck causing increasing tracheal obstruction. A clinical diagnosis of Hashimoto thyroiditis had been made, and sulfonamides and penicillin were administered for one week. Growth of the cervical mass caused increasing respiratory obstruction and necessitated an emergency tracheotomy. Only the isthmus and portions of the enlarged lateral thyroid lobes were resected at this time. Extreme adherence of the thyroid gland to the adjacent muscles was observed. Postoperatively, external x-ray irradiation was administered daily for twenty days through three 10×10 cm. ports on the anterior aspect and both sides of the neck. Each port re-

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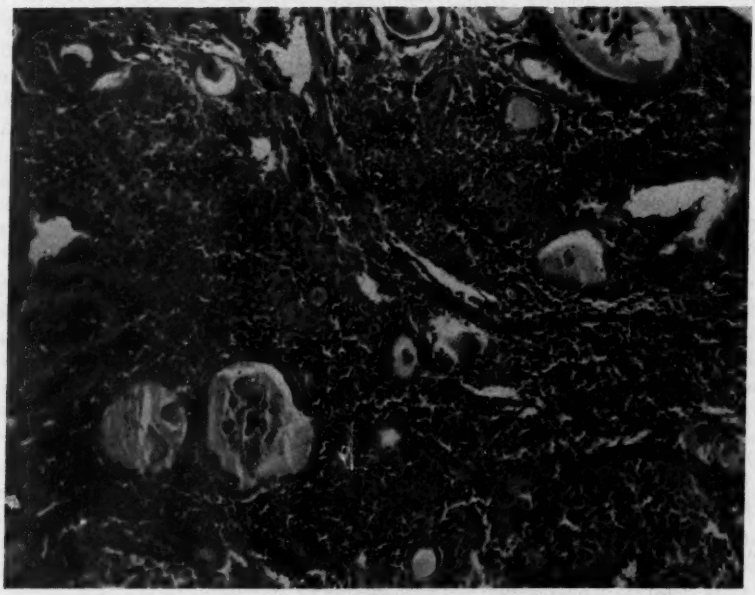

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FIG. 1. (Case 1). The majority of neoplastic cells are reticuloendothelial and stem cells. Note large, multinucleated cells resembling Reed-Sternberg cells. Hematoxylin & eosin; ×250.

FIG. 2. (Case 1). Residual thyroid parenchyma showing lesions of Hashimoto disease. The infiltrating cells are mature lymphocytes. Hematoxylin & eosin; ×125.

ceived 2,000 r in air. Within one and one-half months, the thyroid gland had become almost normal in size. The patient was entirely well for three months following thyroidectomy; then dyspnea and right thoracic pain developed and thyroid enlargement recurred. Examination showed massive right pleural effusion and mediastinal shift to the left. Little symptomatic relief was obtained from several thoracenteses. External x-ray irradiation was administered to the chest (200 r in air to each of two 15.0×15.0 cm. ports in two courses). The white blood cell count and differential count were normal at this time. A hard, fixed swelling, 2.0 cm. in diameter, appeared in the middle third of the left clavicle. Numerous lymph nodes, 1.0 to 2.0 cm. in diameter, were palpable in each axilla. The course during the next month was gradually downhill. The axillary and inguinal lymph nodes enlarged rapidly to 3.0 or 4.0 cm. in diameter. The white blood cell count rose to 100,000 per cu. mm., with 93 per cent immature lymphocytes and 7 per cent neutrophilic leukocytes. On the day of death the white blood cell count was 46,000 per cu. mm. Death occurred nine months after the onset of thyroid enlargement. An autopsy was not performed.

The thyroid biopsy specimen (S46-631) consisted of firm, pale, rubbery, homogeneous tissue. The thyroid glandular tissue had been entirely replaced by neoplastic lymphoid cells which extended through the capsule and invaded the adjacent fat and striated muscle. The predominant cell was a lymphoblast. The nuclei had a coarse chromatin network and a distinct nuclear membrane surrounded by a narrow zone of cytoplasm. A few lymphoid stem cells with large, pale nuclei, distinct nuclear borders, and a single prominent nucleolus were present in smaller numbers. Small numbers of mature lymphocytes were also observed. Mitotic figures were numerous. There were large, poorly demarcated zones of necrosis in which nuclear particles were still visible. A diffuse, delicate, and scanty reticulum network enveloped the neoplastic cells.

Case 3

An 80-year-old white woman had painless diffuse progressive swelling in the thyroid region for four months, associated with a nonproductive cough and respiratory wheezing. The thyroid gland was approximately three times the normal size and was firm and without nodules. There was pronounced enlargement of the isthmus, and the right lobe was larger than the left. There was no bruit. The white blood cell and differential counts were normal. The clinical diagnosis was nontoxic nodular goiter. A subtotal thyroidectomy was performed. The gland was enlarged, firm, rubbery and intimately adherent to all surrounding structures. There was invasion of the sternothyroid muscles. Postoperatively, external x-ray irradiation was administered for seventeen days (2,500 r at a depth of 3.0 cm.). Following completion of irradiation therapy, moderate dysphagia and hoarseness developed and the residual thyroid tumor decreased only slightly in size. The patient is alive ten months after the onset of the goiter, but the course is gradually downhill. The white blood cell and differential counts have not changed.

The specimens (SP54-3174) removed surgically consisted of the right lobe of the thyroid, which measured 10.0×5.0×4.5 cm. and weighed 104 grams (Fig. 3), and a portion of the left lobe, which measured 4.0×3.0×2.0 cm. and weighed 13 grams. No capsule was apparent on the right lobe, whereas the anterior aspect of the left lobe was covered by a thin smooth capsule. Both lobes were composed of pale, greyish-yellow, homogeneous, rubbery tissue with irregular lobulation.

Most of the thyroid glandular tissue was replaced by neoplastic lymphoid tissue which extended through the thyroid capsule and infiltrated the adjacent fat and striated muscle. The lymphoid tissue appeared in broad sheets, with some tendency toward

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4

FIG. 3. (Case 3). Enlarged right lobe extensively replaced by neoplastic lymphoid tissue having a lobulated structure; ×3/5.

FIG. 4. (Case 3). Thyroid parenchyma at margin of neoplasm of right lobe. The epithelial cells are enlarged and pleomorphic, and have abundant eosinophilic cytoplasm. Hematoxylin & eosin; ×250.

cellular grouping. A few focal necrotic areas were present. The predominant cell was a lymphoblast possessing a slightly larger nucleus than that of a mature lymphocyte. The nuclear borders were distinct, and small nucleoli were present. The cytoplasm was scanty and poorly defined. Fewer mature lymphocytes and clasmatocytes were observed. Stem cells were few in number. Mitotic activity was moderate. A diffuse, moderately abundant reticulum network was observed.

A narrow segment of residual thyroid parenchyma lay at the periphery of the right lobe, partly separated from the neoplasm by a fibrous septum, although elsewhere the thyroid parenchyma and neoplastic tissue merged. The thyroid tissue consisted of small groups of abnormal follicles generally formed by large cells with nuclei of variable size and abundant eosinophilic granular cytoplasm (Fig. 4). These thyroid follicles were surrounded by abundant lymphoid tissue consisting of mature lymphocytes. The latter and the neoplastic cells intermingled at the margin of the neoplasm. Several small lymph nodes lying immediately adjacent to the thyroid capsule displayed moderate reticuloendothelial hyperplasia, but were free of neoplastic lymphoid tissue.

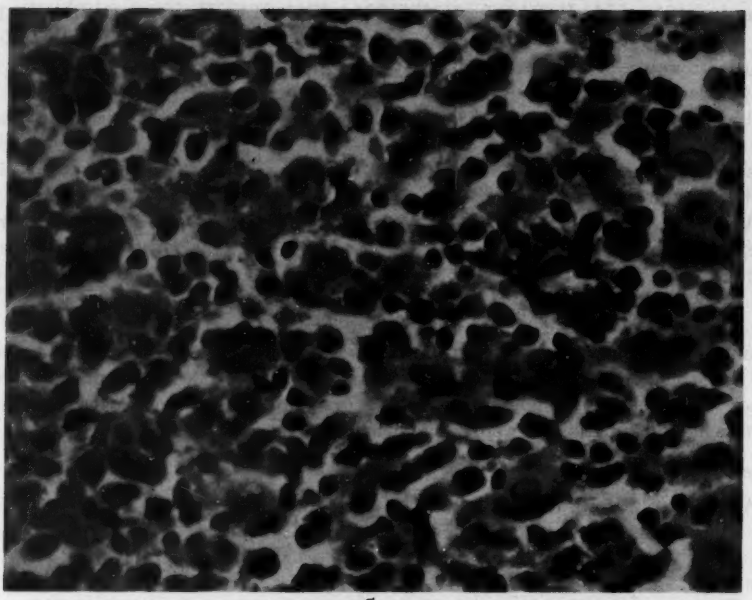
Case 4

A 78-year-old white woman first noted a mass in the lower, anterior right portion of the neck six weeks before admission to the hospital. Progressive growth of the lesion caused respiratory difficulty, hoarseness, and dysphagia. The right lobe of the thyroid gland was three times larger than normal and was hard, immovable, and slightly tender. The isthmus and the left lobe were slightly enlarged; the trachea deviated to the left. The white blood cell count was 9,450 per cu. mm., with 52 per cent neutrophilic leukocytes, 36 per cent lymphocytes and 11 per cent monocytes. The clinical diagnosis was nontoxic nodular goiter, although carcinoma or thyroiditis was considered. A subtotal thyroidectomy was performed. The right lobe was intimately adherent to the adjacent structures and almost completely encircled the trachea. Both lobes were hard and rubbery, but not vascular. The left lobe was approximately one-third the size of the right. Three weeks postoperatively the patient was hoarse and dyspneic due to partial tracheal constriction and paralysis of the left vocal cord. External x-ray irradiation (4,500 r at 3.0 cm. depth) was administered to the neck. Death from metastases occurred six months after the onset of thyroid enlargement. An autopsy was not performed.

The surgical specimen (SP46-1521) consisted of three portions of thyroid tissue weighing 78 grams. The surfaces were irregularly lobulated. Sectioning showed firm, resilient, pale yellow-pink, homogeneous tissue.

Most of the thyroid gland had been replaced by neoplastic lymphoid tissue arranged in broad amorphous sheets. Extension through the capsule and infiltration into the adjacent fat and striated muscle had occurred. The neoplastic cells were pleomorphic. The predominant cells were lymphoblasts and mature lymphocytes, but stem cells and clasmatocytes were only slightly less numerous (Fig. 5). Reticulum in the neoplasm, demonstrated by impregnation with silver, was delicate and sparse. Small focal areas of necrosis were present. In one area the neoplastic cells were infiltrating between residual thyroid follicles. The intrafollicular colloid retained a normal appearance, and there was no eosinophilic alteration of the remaining thyroid epithelial cells.

Several segments of the thyroid gland not involved by neoplasm displayed hyperinvolutionary, follicular enlargement with formation of small circumscribed nodules. Large segments of these parts of the gland contained abundant lymphoid tissue consisting mainly of mature lymphocytes and displaying distinct follicles with germinal centers. The adjacent thyroid follicles were small, separated by mature lymphocytes, and characterized by epithelial cellular enlargement with abundant eosinophilic cytoplasm.



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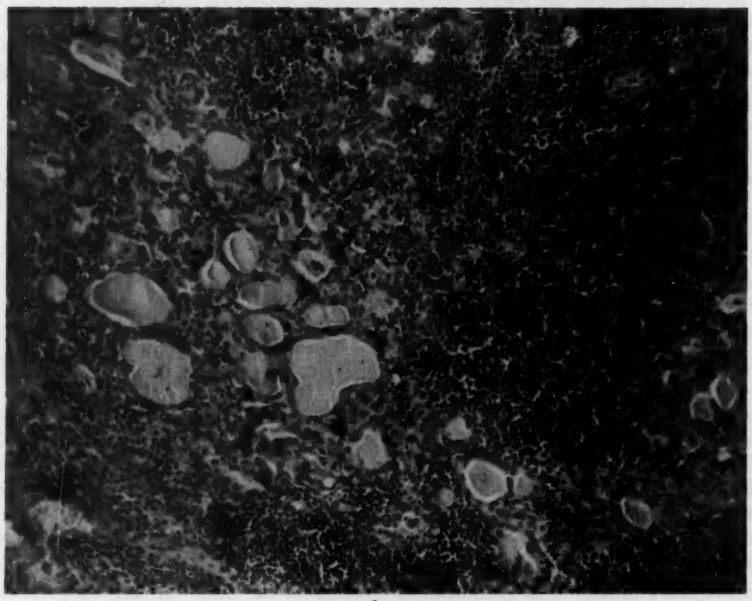

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FIG. 5. (Case 4). The majority of cells are lymphoblasts, but many stem cells, clasmatocytes, and mature lymphocytes are present. Hematoxylin & eosin; ×565.

FIG. 6. (Case 5). Thyroid tissue at periphery of one lobe showing histologic pattern of Hashimoto disease. Hematoxylin & eosin; ×250.

Case 5

A 63-year-old white woman had dyspnea, hoarseness, and a productive cough for seven months. Four weeks before entering the hospital she noted a thyroid mass, which had since gradually increased in size. The left lobe of the thyroid was enlarged, movable, firm, and nontender. It was fixed to the surrounding tissues and caused tracheal deviation to the right. A small, firm, movable nodule was palpable near the upper pole of the left lobe. Enlargement of the right lobe was less pronounced. A small discrete nodule was felt in the isthmus. The left lobe extended retrosternally. There was adductor paralysis of the left vocal cord. The serum protein-bound iodine level was 15.8 micrograms per 100 ml. The white blood cell count was 8,600 per cu. mm., with 30 per cent neutrophilic leukocytes and 60 per cent lymphocytes. The clinical diagnosis was carcinoma of the thyroid gland.

A thyroidectomy was performed, total on the left and subtotal on the right. The entire thyroid gland was diffusely involved by a homogeneous, neoplastic process and was four to five times the normal size. On the left side the neoplasm had invaded the sternothyroid muscle and deep cervical fascia. Several small lymph nodes were found adjacent to the left lobe. The postoperative course was uneventful. Radiation therapy was withheld to be used if the neoplasm should recur. The white blood cell count remained normal, and the lymphocytes varied from 25 to 40 per cent. Two months following operation the patient became hypothyroid and desiccated thyroid was administered. The patient is entirely well eight years after the onset of thyroid disease.

The surgical specimen (SP43-803) consisted of an irregularly enlarged thyroid gland weighing 203 grams. The right lobe measured 9.0 cm. in length, and the left lobe 10.5 cm. The surface was nodular. Sectioning showed greyish-white, soft, fleshy, homogeneous tissue with scattered opaque areas 1.0 to 4.0 mm. in diameter. Two small midline lymph nodes were grossly normal.

Both lobes of the thyroid gland were diffusely and extensively infiltrated by neoplastic lymphoid cells. The thyroid capsule was thick and fibrous; it was intact and almost limited the spreading neoplastic tissue. At one pole the neoplastic lymphoid tissue invaded the adjacent areolar tissue and the peripheral portion of one of several adjacent lymph nodes. Large circumscribed zones of necrosis containing residual degenerating lymphoid nuclei were present in many portions of both lobes.

The predominant neoplastic cell was a lymphoblast possessing a narrow rim of cytoplasm. Fewer mature lymphocytes and numerous lymphoid stem cells also formed part of the infiltrating neoplasm. Few clasmatocytes were noted. Mitoses were not numerous. The reticulum network was scanty, and was usually associated with the blood vessels and residual groups of thyroid epithelial cells rather than with the neoplastic cells.

Poorly defined remnants of the thyroid parenchyma were seen in many portions of both lobes. This tissue generally consisted of small atrophic follicles formed by pleomorphic epithelial cells possessing condensed hyperchromatic nuclei and abundant, homogeneous, eosinophilic cytoplasm. Many of these follicles had been invaded by the neoplastic lymphoid cells. Others contained polypoid groups of epithelial cells. Perilobular fibrosis was often noted about these residual follicles.

In some areas, particularly at the peripheral portions of the lobes, similar abnormal thyroid epithelium was observed (Fig. 6). This was surrounded by abundant lymphoid tissue which was unlike that of the infiltrating neoplasm and consisted of mature lymphocytes often showing formation of distinct lymphoid follicles. This benign lymphoid tissue and the neoplastic lymphoid tissue merged imperceptibly. The small midline lymph nodes did not contain neoplastic tissue.

Case 6

A 46-year-old white woman was well until five months before admission to the hospital, when she noted exertional dyspnea, dysphagia, nocturnal choking, hoarseness, and increased perspiration. Three and a half months before, she had first noticed a hard, painless mass in the left supraclavicular region, which had gradually enlarged to a huge collar-like mass encircling the anterior and lateral aspects of the neck. Two weeks before, she had begun to experience severe, constant pain in the chest and shoulders.

There was pronounced, symmetrical enlargement of the thyroid gland, forming a mass surrounding the anterior and lateral portions of the neck. Lateral extension beneath the sternomastoid muscles into the posterior triangles had occurred, and the enlarged gland bulged from the sternal notch to above the thyroid cartilage. The vocal cords moved normally. The white blood cells varied from 8,200 to 16,800 cells per cu

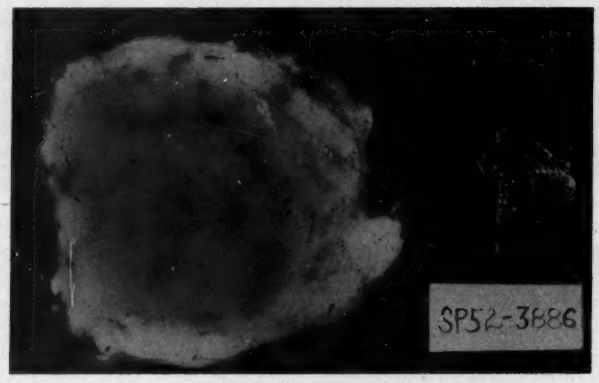


FIG. 7. (Case 6). Greatly enlarged left lobe replaced by neoplastic lymphoid tissue; normal right lobe; ×.8.

mm.; the differential counts were normal. The serum protein-bound iodine level was 6.6 micrograms per 100 ml., and the basal metabolic rate was +41 per cent. The clinical diagnosis was carcinoma of the thyroid gland. Total thyroidectomy was performed. The left lobe consisted of a large, multinodular, firm, homogeneous mass which was adherent to the surrounding muscles. Posteriorly, the mass invaded the prevertebral fascia and the carotid sheath; inferiorly, the neoplasm extended into the mediastinum. The right lobe was grossly normal in size and appearance. No enlarged cervical lymph nodes were found. Postoperatively, external x-ray irradiation of the neck was administered during a period to twenty days. The total tissue dose in the midline of the neck at a depth of 6.0 cm. was 2,400 r. The patient died of extensive metastases twenty-seven days following thyroidectomy and six months after the onset of symptoms. White blood cell and differential counts were not made postoperatively.

The surgical specimen (SP52-3886) consisted of a solid, resilient neoplasm of the left lobe of the thyroid gland, measuring 11.0×8.0×7.0 cm. and weighing 273 grams. The external surface was rough and reddish-brown. Sectioning showed pale yellow-grey, homogeneous tissue. The right lobe measured 4.5×2.5×2.0 cm., weighed 11 grams, and appeared normal (Fig. 7).

The entire left lobe was densely and diffusely infiltrated with neoplastic lymphoid

cells displaying prominent vascular invasion. Compressed segments of thyroid parenchyma were found at the periphery of the left lobe. Thyroid follicles, isolated by the advancing neoplasm, remained in the superficial portions of the tumor. In some follicles the thyroid epithelium was present, but in many the epithelial cells had been replaced by neoplastic lymphoid cells which then lined the follicular spaces (Fig. 8). Some residual thyroid follicles contained neoplastic cells, partially or completely replacing the intrafollicular colloid.

The predominant neoplastic cell was a lymphoblast. The nuclei contained delicate chromatin particles. Some had distinct, small nucleoli. Little cytoplasm was present. Few mature lymphocytes and rare stem cells and clasmatocytes were observed. Mitotic figures were very numerous. The capsule of the left lobe was extensively invaded by the neoplastic cells. Segments of the adherent anterior muscles were invaded and included in the peripheral anterior portions of the neoplasm. Few sarcolemmal nuclei remained. Extensive necrosis and hemorrhage had occurred within the neoplasm, and considerable focal nuclear fragmentation was observed throughout the entire mass.

The neoplasm contained a relatively scanty reticulum network, generally associated with the blood vessels and with the immature stem cells or reticulo-endothelial elements. Most of the cells, *i.e.*, lymphoblasts, showed no formation of reticulum.

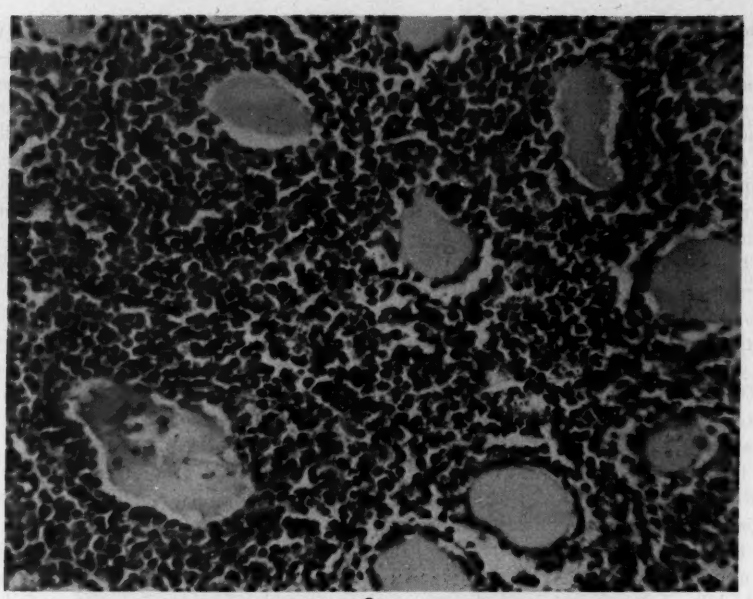
The greater part of the right lobe of the gland was normal in structure, and consisted of uniform follicles of normal size and colloid content. Several large segments of the right lobe showed extensive infiltration with mature lymphoid cells, often in follicular formation, and contained groups of small thyroid follicles or nonfollicular groups of epithelial cells. These epithelial elements were uniform and did not show excessive cytoplasmic eosinophilia (Fig. 9).

At autopsy, nodular masses of soft, grey, neoplastic tissue were found in the myocardium and spleen. Large masses of similar neoplastic tissue filled the retroperitoneal tissue, replacing much of the pancreas. Multiple neoplastic nodules were found throughout the walls of the stomach and bowel; many showed mucosal ulceration. Both kidneys were enlarged; the parenchyma was extensively replaced by ill-defined, confluent masses of grey, firm, neoplastic tissue. This material also infiltrated the renal pelves and ureters. In the pelvis there was abundant neoplastic tissue which had extensively invaded the pelvic viscera. No residual neoplasm was found in the neck. Neoplastic involvement of the heart, lungs, and kidneys was diffuse and resembled leukemic infiltration. Lymph nodes, spleen, and bone marrow were spared.

Case 7

A 66-year-old white woman had recurrent but progressive swelling in the lower anterior portion of the neck for four years. During this period her voice had been husky. For one year she had noted dysphagia, increasing hoarseness, and a sense of fullness in the neck. Three weeks before entry into the hospital, an ovoid mass, 4.0 to 5.0 cm. in diameter, became visible in the right side of the neck.

Examination showed an ovoid, hard, fixed mass, 4.0 cm. in diameter, involving the upper pole of the right lobe of the thyroid gland. The left lobe was of equal size, but was soft and had a lobulated surface. No enlarged lymph nodes were palpable. The vocal cords moved normally. The white blood cell count was 6,000 per cu. mm., with 48 per cent neutrophilic leukocytes and 44 per cent lymphocytes. A total thyroidectomy was performed. The entire gland was diffusely enlarged and firm. The right lobe was extensively involved by a hard infiltrative malignant process, and was intimately adherent to the overlying ribbon muscles. Several enlarged, firm, lymph nodes were found in the



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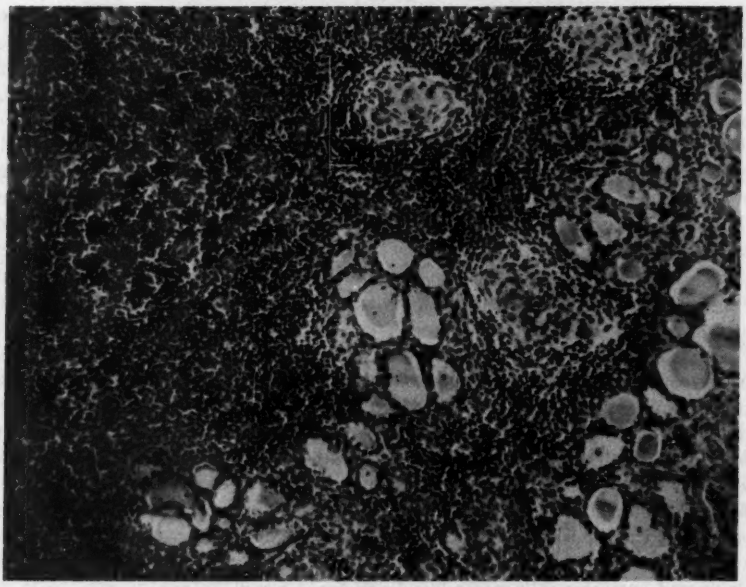

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FIG. 8. (Case 6). Malignant lymphoid cells are isolating thyroid follicles, replacing epithelium, and eventually obliterating the follicles. Hematoyxlin & eosin; ×250.

FIG. 9. (Case 6). Right lobe not involved by neoplasm. The lymphocytes are mature and the epithelial alteration is characteristic of Hashimoto disease. Hematoxylin & eosin; ×125.

suprasternal area and about both lower thyroid poles. External x-ray irradiation was delivered to the neck and mediastinum two months following thyroidectomy. The calculated tumor dose to the lower neck was 3,100 r at 9.0 cm. depth and to the upper mediastinum was 3,000 r at 4.0 cm. depth. Shortly thereafter, the patient appeared hypothyroid and desiccated thyroid was administered. One year after the operation the patient complained of tightness, swelling, and pain in the left side of the lower anterior portion of the neck. Nineteen months postoperatively, there were no evidences of metastases. The serum protein-bound iodine level was 4.9 micrograms per 100 ml. The white blood cell count and differential count remained normal.

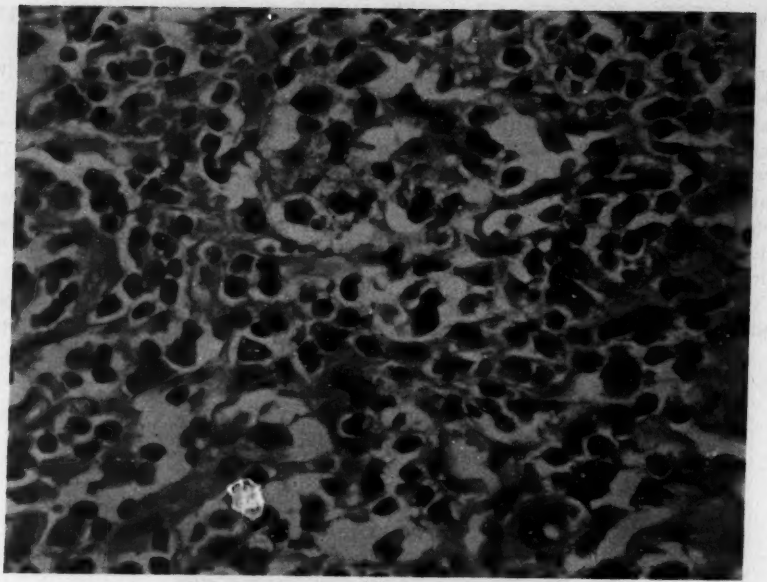
The two thyroid lobes (SP53-3059) weighed 105 grams (Fig. 10). The right lobe measured 7.0×5.0×4.0 cm. and consisted of firm, pale tan, homogeneous tissue. A thin layer

FIG. 10. (Case 7). Both thyroid lobes are enlarged. The left lobe shows fibrous lobular accentuation. Most of the right lobe consists of malignant lymphoid tissue. Note enlarged lymph nodes attached to lower pole of right lobe; ×.7.

of reddish-brown thyroid parenchyma remained at the borders, particularly inferiorly. The left lobe consisted of firm, glistening, reddish-brown tissue with accentuated interlobular septums. Attached to the lower pole of each lobe were several ovoid lymph nodes, 2.0 cm. in diameter.

Most of the right lobe was heavily infiltrated by neoplastic lymphoid tissue, which completely replaced the thyroid parenchyma in the central portion of the lobe. At the periphery, particularly at the upper and lower poles of the right lobe, segments of thyroid parenchyma remained. In most areas the neoplasm was restrained by the thyroid glandular capsule, but anteriorly neoplastic invasion into the adjacent areolar tissue had occurred. No necrosis or hemorrhage was apparent.

The pattern in different portions of the neoplasm varied considerably. In general, the predominant cell was an immature lymphocyte or lymphoblast which appeared slightly larger than a mature lymphocyte and contained a more delicate nuclear chromatin network. These cells possessed abundant eosinophilic cytoplasm. Fewer lymphoid stem cells with distinct single eosinophilic nucleoli and even fewer mature lymphocytes were found in most portions of the neoplasm (Fig. 11). Clasmatocytes were present in small numbers. Mitotic figures were numerous throughout most portions of the neoplastic tissue. The infiltrating neoplasm separated and isolated the thyroid follicles and eventually invaded the follicular lumens, causing fragmentation and final disappearance of



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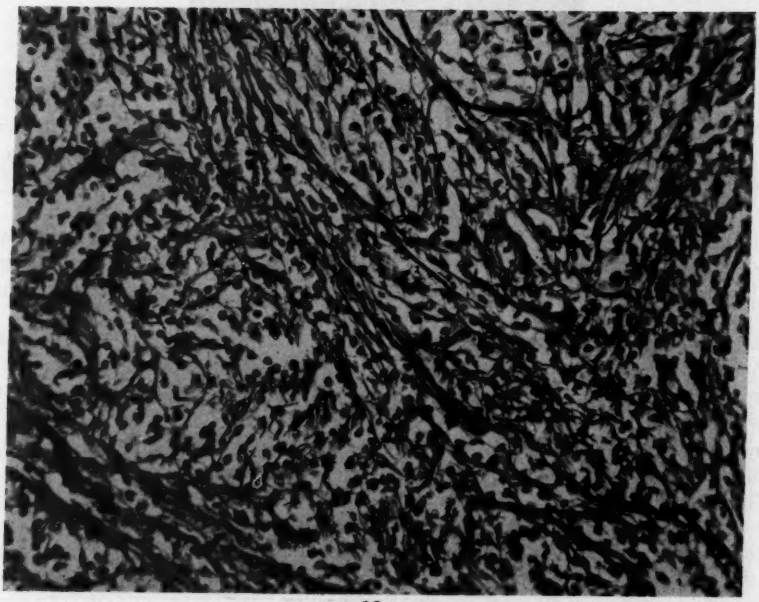

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FIG. 11. (Case 7). A variety of lymphoid cells are present but lymphoblasts predominate. Hematoxylin & eosin; ×565.

FIG. 12. (Case 7). Moderately rich reticulum network in malignant lymphoma of thyroid gland. Laidlaw connective-tissue stain; ×250.

thyroid colloid. Some invaded follicles, however, retained thyroid epithelium until their outlines were completely obscured in the dense neoplastic tissue.

A moderately rich reticulum network was present. The fibrillary material was more abundant where the less mature lymphoid stem cells, reticulo-endothelial cells, and fibroblasts were concentrated. Where reticulum was most dense a few collagenous fibers had appeared (Fig. 12).

In the right lobe, the residual thyroid parenchyma surrounding the neoplasm was abnormal. As a rule, the follicles were enlarged and distended with colloid. The thyroid epithelial cells were cuboidal and characterized by a moderate degree of nuclear hyperchromatism and pleomorphism and cytoplasmic eosinophilia. Most of the lobules contained large, benign lymphoid collections consisting of lymphoid follicles with large germinal centers. Usually the thyroid parenchyma in the areas showing the greatest lymphoid infiltration were characterized by small clusters of thyroid follicles, many of which were devoid of colloid. The cells of these follicles were quite pleomorphic and showed nuclear enlargement and an abundance of eosinophilic cytoplasm. The most peripheral portions of the right lobe were completely free of infiltrating tissue. Groups of small thyroid follicles surrounded by a considerable amount of collagenous stroma were seen near the infiltrating neoplasm.

The thyroid parenchyma of the left lobe closely resembled that remaining at the periphery of the right lobe. Follicular enlargement with general epithelial cellular hypertrophy and eosinophilia were characteristic. Considerable amounts of benign lymphoid tissue, consisting mainly of mature lymphocytes, were present and occasional lymphoid follicles were seen throughout this lobe. The thyroid follicles in the areas most densely infiltrated with lymphoid tissue were usually small, often devoid of colloid, and showed typical changes of "exhaustion."

The normal architecture of most of the enlarged lymph nodes lying below the lower pole of the right lobe had been destroyed by infiltrating neoplastic lymphoid cells which had the same characteristics as those in the left lobe. Extension through the capsule of the lymph nodes into the surrounding adipose tissue had also occurred.

Case 8

A 49-year-old white woman during late adolescence had a goiter which disappeared following administration of iodized salt. Two months before entry into the hospital, enlargement of the neck was noted and Lugol's solution was administered by her physician. There was progressive enlargement of a mass in the lower, anterior neck associated with mild weight loss, an increase in the pitch of her voice, a feeling of warmth, dysphagia, and discoloration of the skin overlying the cervical mass.

Examination disclosed a mass in the anterior and anterolateral portions of the neck in the region of the thyroid gland. This obliterated the suprasternal space, and seemed adherent to the overlying muscles. The overlying skin appeared erythematous and tense. The mass had the configuration of a normal thyroid and generally was smooth, although it did not move with deglutition. Tender nodules were palpable in the upper and lower poles of the left lobe of the thyroid. The right lobe was larger than the left. There was no bruit. Function of the vocal cords was impaired, but there was no evidence of nerve involvement. The white blood cell count was 6,800 per cu. mm., with 77 per cent neutrophilic leukocytes and 20 per cent lymphocytes. The serum protein-bound iodine level was 7.4 micrograms per 100 ml. The clinical diagnosis was carcinoma of the thyroid gland.

Surgical exploration showed that the mass had extensively invaded the ribbon muscles of the neck. It consisted of soft, semigelatinous, greyish-white to greyish-red vascular tissue densely fixed to the trachea, vascular sheaths, and inferiorly to the clavicles.

The isthmus and a portion of the right lobe were resected, and a tracheotomy performed. Five days postoperatively x-ray irradiation to the neck was begun (1,975 r in air). Within two weeks the patient complained of severe pain in the left hip; the mass in the neck, however, had gradually decreased in size. Shortly thereafter, the patient manifested neurologic signs of metastases to the lumbosacral plexus, first on the right and then on the left. The white blood cell and differential counts were not abnormal. The patient deteriorated rapidly, although the thyroid mass was decreasing in size. Death occurred three months following the onset of thyroid enlargement and one month following partial thyroidectomy. An autopsy was performed.

The tissue received (67894) after the partial thyroidectomy was soft, edematous, and greyish-red. Normal thyroid parenchyma was not observed.

Most of the thyroid tissue was extensively infiltrated by neoplastic lymphoid cells which extended into the lateral portions of the isthmus, perforated the thyroid capsule and infiltrated the surrounding adipose and vascular tissues. The neoplasm contained a few small zones of necrosis, which were infiltrated with neutrophilic leukocytes.

The cellular pattern of the neoplasm was uniform. The predominant cell was the lymphoblast with a pleomorphic nucleus and usually two to three distinct irregular nucleoli. The nuclear membranes were distinct; the nuclear chromatin network was sparse and delicate. The cytoplasm of these cells was more abundant than that of a mature lymphocyte, and was homogeneous and eosinophilic. Mature lymphocytes were present in small numbers (Fig. 13). Clasmatocytes and stem cells varied in number in different portions of the tumor. In some areas, particularly where the neoplasm was infiltrating the adjacent striated muscle, immature stem cells were uniformly scattered among the lymphoblasts. Unusually numerous mitoses were observed.

The reticulum network in the neoplastic tissue was sparse and usually was associated with the capillary walls or the thyroid follicles remaining at the advancing margin of the neoplasm.

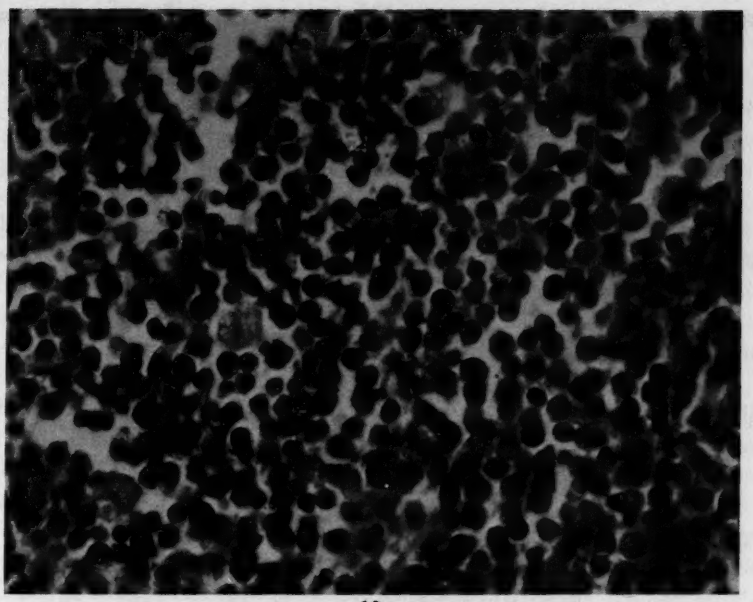
At the junction of the two lobes and the isthmus the neoplasm was infiltrating into the thyroid parenchyma. Thyroid follicles were isolated and surrounded by the infiltrating lymphoid cells, and follicular spaces were distended with neoplastic cells which replaced the colloid. Thyroid epithelium persisted near the margins of the neoplasm, even after the follicular space had become completely filled with neoplastic tissue. These remaining thyroid cells did not display nuclear pleomorphism or cellular eosinophilia.

The thyroid tissue of part of the isthmus consisted of uniform thyroid follicles lined by low cuboidal epithelial cells, and contained normally staining colloid. Throughout this segment of tissue, however, portions of the lobules consisted of small thyroid follicles containing pale or no colloid, or small nonfollicular groups of thyroid epithelial cells. These cells appeared normal and only rarely displayed nuclear hyperchromatism, pleomorphism or cytoplasmic eosinophilia. In these portions of the lobules were groups of infiltrating mature lymphocytes and a few small distinct follicles with germinal centers.

Autopsy (A4197) showed extensive lymphosarcomatosis involving the thyroid, pancreas, gastro-enteric tract, cervical and retroperitoneal lymph nodes, pancreas, kidneys, liver and right ovary. Infiltration of neoplastic cells in the kidney (Fig. 14) and bone marrow was diffuse and characteristically leukemic, whereas the hepatic infiltration was limited to the subcapsular zone. The thyroid neoplasm had the same pattern as that of the surgical specimen. No changes due to irradiation were observed.

COMMENT

Five of the 8 patients described in this report were seen by members of the Thyroid Clinic at the University of California Hospital between 1920



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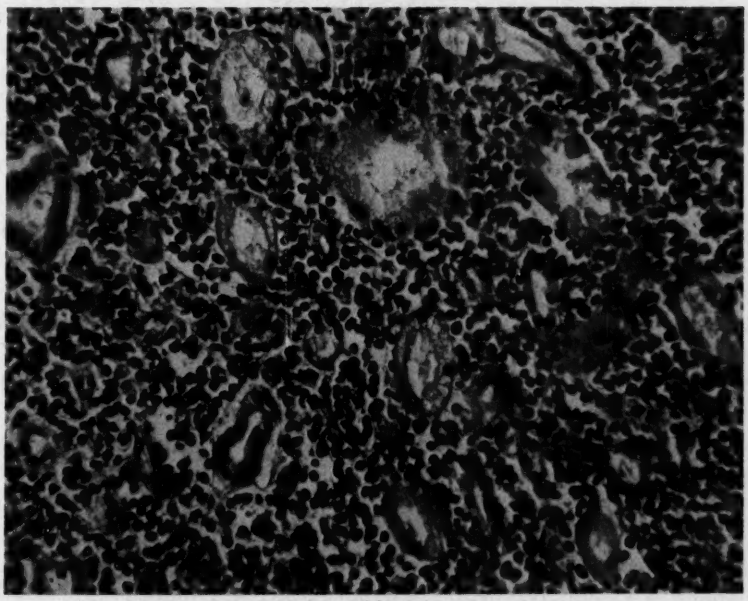

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FIG. 13. (Case 8). Closely packed malignant lymphoid cells. Majority are lymphoblasts, but many mature lymphocytes are present, Hematoxylin & eosin; ×565.

FIG. 14. (Case 8). Neoplastic lymphoid infiltration in kidney, appearing leukemic. Hematoxylin & eosin; ×250.

TABLE 1

Patient			Symptoms and duration	Physical findings	Surgical findings	Cervical lymph node metastases	Distant metastases	Treatment	Survival after onset
Case No.	Sex	Age (yrs.)							
1	M	73	Firm swelling in neck—1 mo.	Symmetrically enlarged, hard thyroid gland	Dense adherence to surrounding cervical tissues; many enlarged cervical nodes	Yes	No	Subtotal thyroidectomy; irradiation	Died, 10 mos.
2	M	21	Stiffness and swelling of neck and increasing respiratory obstruction—1 mo.	Bulky, diffusely enlarged, firm thyroid gland	Invasion of surrounding muscles	Yes	Yes	Resection of isthmus and portions of lateral lobes; tracheotomy; irradiation	Died, 9 mos.
3	F	80	Painless, diffuse swelling of neck with cough and respiratory wheezing—4 mo.	Firm, enlarged thyroid gland, 3× normal size; right lobe>left	Firm, rubbery gland with adherence and invasion of surrounding tissues	No	No	Subtotal thyroidectomy; irradiation	Alive, 10 mos. Residual tumor present
4	F	78	Rapidly growing mass in neck with hoarseness, dysphagia and dyspnea—6 wks.	Hard, fixed right thyroid lobe; slight enlargement of isthmus and left lobe	Hard, resilient gland; right lobe adherent and encircling trachea; intimately adherent	No	Yes	Subtotal thyroidectomy; irradiation	Died, 6 mos.
5	F	63	Dyspnea, hoarseness, and productive cough—7 mos. Growing thyroid mass—4 wks.	Both lobes enlarged, rubbery, and fixed; left > right	Diffuse involvement of gland by neoplasm; gland 4–5× normal size; invasion of muscle	Yes	No	Subtotal thyroidectomy	Alive and well, 8 yrs.
6	F	46	Dyspnea, dysphagia, nocturnal choking and hoarseness—5 mos. Painless mass in neck—3½ mos.	Bilateral, extreme thyroid enlargement	Left lobe greatly enlarged and adherent; right lobe normal	No	Yes	Total thyroidectomy; irradiation	Died, 6 mos.
7	F	66	Progressive swelling of neck and hoarseness—4 yrs. Dysphagia—1 yr. Mass in neck—3 wks.	Hard, fixed mass in right thyroid lobe; left lobe of equal size but softer	Right lobe hard, enlarged and adherent; enlarged lymph nodes near both lower poles	Yes	No	Total thyroidectomy; removal of local cervical lymph nodes; irradiation	Alive and well, 19 mos.
8	F	48	Progressive enlargement of neck, voice change, and weight loss—2 mos.	Diffuse thyroid enlargement with fixation and erythema of overlying skin; right lobe >left	Soft, gelatinous, grey-red, vascular tissue, adherent to surrounding tissues	No	Yes	Exploration of thyroid; partial thyroidectomy; irradiation	Died, 3 mos.

and 1955. During this same period, 313 carcinomas were observed in a total of 7,865 thyroidectomies. The other 3 patients in this study (Cases 1, 2 and 8) had been treated in nearby hospitals. Thus, the incidence of malignant lymphoma of the thyroid gland in the University of California series is 0.06 per cent.

The significant clinical data in these 8 cases are summarized in Table 1. All but 2 of the patients were female. Their ages ranged from 21 to 80 years. With the exception of 1 patient who had a goiter for four years, all had thyroid enlargement for exceedingly brief periods. These tumors had increased rapidly in size, usually with the concurrent development of pressure effects. All patients were euthyroid.

The thyroid glands in this group of patients were enlarged either unilaterally or bilaterally, were firm or hard, and usually were adherent and immovable. The surfaces had rounded contours, and only 1 contained palpable nodules.

When the historical and physical findings were interpreted, no diagnosis other than thyroid malignancy was tenable. The diffusely enlarged glands of classic Hashimoto disease (4) occur as a rule in younger female patients and usually are of longer duration. They less often produce pressure symptoms and are of a softer and more resilient consistency. Although often adherent, they lack the pronounced fixation of the gland invaded by malignant lymphoma. At times a hard, fixed thyroid gland may be observed in the late stages of subacute thyroiditis (5), but a history of recent growth would be lacking, pressure effects less severe, and the thyroid enlargement much less than in malignant lymphoma. The antecedent history of acute disease with fever and migrating tenderness in the gland should make the diagnosis of subacute thyroiditis evident. A rapidly growing, anaplastic carcinoma of the thyroid gland, usually observed in older individuals, would be difficult or impossible to differentiate clinically from malignant lymphoma. Most other thyroid carcinomas appear as nodular goiters, whereas nodules are infrequently observed in malignant lymphoma of the thyroid gland. Palpable cervical lymph nodes are commonly present with papillary thyroid carcinoma, but cervical nodes were not palpable in the present group of patients with malignant lymphoma.

Five of the 8 patients were dead three to ten months after the clinical onset of the disease. Four deaths resulted from disseminated disease (1 from lymphatic leukemia), and 1 from local obstruction. Of the 3 surviving patients, 1 has a residual thyroid tumor (six months after thyroidectomy) which has not responded to irradiation, but 2 have no evidence of recurring disease nineteen months and eight years, respectively, after the clinical onset of disease. Both had evidences of local invasion of the perithyroidal tissue at operation. The patient who has survived eight years underwent only subtotal thyroidectomy and received no irradiation.

The thyroid neoplasms of all 8 patients consisted of a variety of pleomorphic lymphoid cells ranging from undifferentiated reticulo-endothelial cells to mature differentiated lymphocytes. The predominance of various cellular types varied considerably in different portions of each tumor, so that precise classification based on a single type of lymphoid cell (6) was not possible. In general, however, the neoplasms in the majority of patients consisted mainly of closely packed, immature lymphoid cells with the characteristic structure of lymphoblasts. Mitotic activity was generally pronounced. These tumors were characterized by the sparse reticulum network which was closely related to the capillaries and the few immature lymphoid and reticulo-endothelial cells present.

The neoplasms in 3 of the patients had a looser arrangement of the neoplastic cells. Although lymphoblasts were slightly more numerous than any other single cellular type, much larger numbers of reticulo-endothelial cells, fibroblasts, and clasmatocytes were present. In these 3 tumors, fibrillary intercellular substance, both reticulum and collagen, was more plentiful and widely distributed. Multinucleated neoplastic cells, resembling Reed-Sternberg elements, were observed in only 1 of the tumors, and the general pattern was not that of Hodgkin's granuloma.

There was no correlation in this small group of patients between the cellular pattern, number of mitoses, or reticulum content of the neoplasm and 1) the clinical duration or course of the disease, 2) the extent of local aggressiveness or metastatic dissemination of the neoplasm, or 3) the response to irradiation. The pathologic processes in the surviving patients were indistinguishable from those in the fatal group. Brewer and Orr (3) have suggested that some thyroid lesions generally regarded as reticulosarcoma or lymphosarcoma may in reality represent an unusual type of granulomatous disease with a predilection for the thyroid gland and gastroenteric tract. This combination was a prominent feature in 2 cases in the present study (Cases 6 and 8). Gall and Mallory (6) indicated that malignant lymphoma with a single primary lesion of a viscus (gastro-enteric tract or thyroid gland) offered a better prognosis than a similar lesion originating in lymph nodes.

The invasive malignant lymphoid tissue extended peripherally through the thyroid interstitial tissue. Near the center of the involved lobes, a few thyroid epithelial cells remained, whereas at the periphery, isolated thyroid follicles were usually present. Neoplastic lymphoid cells gradually replaced follicular epithelium, while colloid was still present. Eventually colloid too was replaced by neoplastic cells, although the supporting follicular reticulum seemed to survive for a time. In some instances the thyroid capsule partially limited extraglandular spread of the neoplasm, but invasion of adjacent areolar tissue or skeletal muscle had occurred in all 8 cases. Malignant lymphoid cells rarely invaded lymphatic or vascular

channels, which perhaps explains the infrequent dissemination to regional lymph nodes. The extent of necrosis and hemorrhage within the neoplastic tissue was similar to that usually seen in malignant lymphoma originating in other sites. No changes in the neoplastic tissue which could be ascribed to irradiation were demonstrable in the one thyroid gland examined at autopsy (Case 8) following x-ray therapy.

The simultaneous occurrence of a malignant lymphoma and the classic lesions of Hashimoto disease (4) in 7 of the 8 cases in this study indicates a significant relationship between the two processes. A similar relationship exists between thyroid epithelial neoplasms and Hashimoto disease (7). The Hashimoto process was diffuse in 4 instances and focal in 3. It was observed in thyroid lobes uninvolved by the neoplasm and in residual segments of thyroid lobes invaded by the lymphoid neoplasm. These Hashimoto lesions displayed characteristic epithelial alterations, as well as diffuse or focal lymphoid infiltration (4). The clinical and pathologic data in Case 7 in this study indicated that the onset of a growing thyroid neoplasm one year before had been preceded by thyroid enlargement of four years' duration, caused by hyperinvolution and extensive Hashimoto disease.

Although the benign lymphoid tissue and the neoplastic lymphoid tissue in most of the cases usually merged into one another, the two had distinctly different histologic and cytologic features. Cellular pleomorphism, mitotic activity, and aggressive invasion characterized the malignant lymphoid tissue, whereas formation of lymphoid follicles and a close relationship to small thyroid follicles with Askanazy changes in the epithelial cells were typical of the Hashimoto process.

Hashimoto (8), Williamson and Pearse (9), Joll (10), and Ewing (11) all stressed the histologic similarities of the two lesions. It should be emphasized that invasion of the thyroid gland by malignant lymphoid tissue originating either in the gland or in adjacent cervical lymph nodes does not cause thyroid epithelial alteration characteristic of the lesions of Hashimoto disease (4).

The relationship between these two thyroid processes has been discussed previously. Graham (12) cited a case of thyroid lymphosarcoma believed to have originated in struma lymphomatosa. The observations of Rice (13) gave no definite support to the theory that lymphosarcoma might develop from chronic thyroiditis, but the possibility could not be excluded. Adé (14) described a lymphosarcoma of the thyroid in a 70-year-old woman with myxedema, whose gland showed chronic atrophic thyroiditis. Infiltration by lymphocytes and plasma cells was destroying the thyroid follicles. Kellett and Sutherland (2) concluded that lymphosarcoma probably developed in the lymphoid hyperplasia so common in the thyroid glands of elderly females, rather than from a pre-existing struma lymphomatosa.

Lymphoid hyperplasia is common in the thyroid gland, especially in

advancing age and in women. In our experience, focal lymphoid hyperplasia of the thyroid is often associated with epithelial disease characteristic of Hashimoto disease as well, and may be observed both in surgical and autopsy material. The occurrence of focal Hashimoto disease is more frequent than is generally appreciated (4). It seems likely that malignant lymphoma may originate in proliferating thyroid lymphoid tissue, with or without associated thyroid epithelial disease.

SUMMARY AND CONCLUSIONS

1. Eight cases of malignant lymphoma (lymphosarcoma) of the thyroid gland are described.

2. Six of the 8 patients were women whose ages ranged from 46 to 80 years. The majority had rapidly growing, large goiters and concurrent pressure symptoms.

3. Five of the 8 died three to ten months after the clinical onset of thyroid disease, despite surgical and radiation therapy. Three patients have survived ten months, nineteen months and eight years, respectively.

4. The thyroid glands of 7 of the 8 patients also displayed the lesions of Hashimoto disease. It was concluded from this study that a significant relationship exists between these two processes.

Acknowledgments

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STUDIES IN NON-MYXEDEMATOUS HYPOMETABOLISM

I. THE CLINICAL SYNDROME AND THE EFFECTS OF TRIIODOTHYRONINE, ALONE OR COMBINED WITH THYROXINE*†

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THE diagnosis of classic primary myxedema usually offers little difficulty and the results of therapy with desiccated thyroid or thyroxine are striking and gratifying. Such patients, however, constitute only a small fraction of all individuals who demonstrate significant depression of the basal metabolic rate. Hypometabolism also accompanies hypopituitarism, hypogonadism, Addison's disease, nephrosis, markedly reduced activity, and malnutrition. When all such causes of hypometabolism have been excluded, however, there remain a large number of individuals with basal metabolic rates of −20 to −30 per cent who do not appear to be myxedematous and who are not improved by the administration of desiccated thyroid. The cause of the low basal metabolism in them is obscure.

The existence of this group of patients was recognized by Plummer as early as 1917 (1) and attention has been called to their clinical characteristics by many subsequent authors under the title "low basal metabolism without myxedema" (2, 3) or "euthyroid hypometabolism." There has been a remarkable similarity in all clinical descriptions of these patients. The most frequent complaints have been lethargy, easy fatigability, nervousness, irritability, emotional instability, sensitivity to cold, headache, ill defined skeletal plain, diminished sexual potency in the male and menstrual irregularity in the female. The lack of specificity of the complaints has often led to a diagnosis of neurosis. In contrast to true hypothyroidism,

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such cases demonstrate one or more of the following (4): (i) in the vast majority, a failure of the basal metabolic rate to rise to normal levels after desiccated thyroid, even when administered to the point of toxicity; (ii) in the few instances in which the metabolic rate becomes elevated toward normal, absence of clinical improvement in signs and symptoms; (iii) lack of ultimate beneficial effects in such patients, with progressively increased thyroid dosage (5); and (iv) in all cases, the necessity for a large dose of thyroid to raise the metabolic level, compared to that required to restore a truly myxedematous patient to a euthyroid state.

Several explanations have been considered for this seeming paradox of low basal metabolic rate, non-responsive to desiccated thyroid, occurring in the presence of normal thyroid function and accompanied by vague symptoms suggestive of hypothyroidism. It has been regarded as "physiologic-hypometabolism," such patients being represented in the lower half of a normal distribution curve of oxygen consumption (6). Some authors suggest that the non-myxedematous hypometabolic rate is consequent to end-organ insensitivity (insensitivity of the thyroid gland to the action of thyrotropin (7)) or to general body tissue insensitivity to the thyroid hormone (8). Others propose that the thyroid hormone is destroyed, stored or inactivated rapidly in such patients (9). It has also been suggested that gastrointestinal absorption of desiccated thyroid may be deficient.

When our studies of thyroid function—including determinations of the serum protein-bound iodine, serum cholesterol, thyroidal I^{131} uptake and turnover, and the release of I^{131}-labelled hormone—in a group of such patients confirmed that it was at a normal level, we considered the possibility that such patients were unable to utilize thyroxine, *i.e.*, convert it to an active form and metabolize it. This concept suggested the use of another potent thyroid substance, *l*-3:5:3′-triiodothyronine, in such patients.

CLINICAL MATERIAL

Four male patients, 29 to 47 years of age, were studied (Table 1). Basal metabolic rate measurements were made in duplicate at frequent intervals, to obtain a reliable level before any change in regimen. The basal metabolic rate before treatment ranged from -20 to -25 per cent. The 24-hour thyroidal I^{131} uptake ranged from 23 to 33 per cent (normal, 30 ± 5 per cent) (10). The serum protein-bound iodine level (11) ranged from 5.0 to 6.0 micrograms per 100 ml., and the serum cholesterol level (12) from 180 to 246 mg. per 100 ml. The history and physical appearance were notably similar in all cases. The presenting difficulty was usually lack of energy, fatigue, and somnolence. In addition, 3 of the 4 men complained of nervousness, irritability, easy weight gain, constipation, aching of the muscles and joints, and sensitivity to the cold. In 3 of the 4, diminished

TABLE 1. THE PRETREATMENT CLINICAL DATA IN CASES I–IV

Patient	Age	Sex	B.M.R. (%)	Thyroidal 24-hr. I^{131} uptake, %	Serum PBI (μg./100 ml.)	Serum chol. (mg./100 ml.)
1. R.B.	29	M	−25	33	5.0	230
2. W.G.	38	M	−20	23	6.0	246
3. H.H.	46	M	−25	25	—	195
4. H.Z.	47	M	−25	32	5.5	180

potency was also mentioned. On examination, the face was sallow and pasty and periorbital puffiness was common. There was no myxedema or loss of hair, and the skin was soft, though cool and moist.

RESULTS

The metabolic responses of these patients to the oral administration of *l*-thyroxine, *l*-triiodothyronine and mixtures of these compounds are illustrated in the following case reports:

Case I

R.B., a 29-year-old male had suffered from a "tired and logy" feeling during the previous three to four years. His physician had prescribed increasing doses of desiccated thyroid and during the two years before study, 5 grains of desiccated thyroid daily had been administered. On this dosage, the patient complained of insomnia, palpitation, warmth and perspiration; the basal metabolic rate was +20 per cent, the serum cholesterol level was 187 mg. per 100 ml., and the 24-hour thyroidal uptake of a tracer dose of I^{131} was 5 per cent.

During the next six months, following omission of all medication, the basal metabolic rate varied from −26 to −30 per cent. The 24-hour thyroidal I^{131} uptake was 33 per cent. The patient still complained of a logy feeling and tiredness. Again, ten months later, still without thyroid medication, the basal metabolic rate was −25 per cent, and the serum cholesterol level ranged from 227 to 253 mg. per 100 ml. The serum protein-bound iodine level was 5.0 micrograms per 100 ml.

The experimental data are illustrated in Figure 1. L-thyroxine,[1] 0.1 mg. daily for four weeks and 0.2 mg. daily for the subsequent three weeks, did not alter the clinical state. The average basal metabolism was −25 per cent, and the serum cholesterol level remained at 227 mg. per 100 ml. The *l*-thyroxine was omitted, and the next day *l*-triiodothyronine was started in a daily dosage of 70 micrograms, administered for four and a half weeks. There was only a slight rise in the basal metabolic rate; the serum cholesterol level was 226 mg. per 100 ml. The dose of *l*-triiodothyronine was increased to 105 micrograms daily; during the ensuing thirty-five days, there occurred a progressive increase in the basal metabolic rate to −5 per cent. The serum cholesterol level fell only slightly, to 195 mg. per 100 ml. During this period, the patient was alert and active and stated

[1] L-thyroxine (Elthrin) and tablets of *l*-triiodothyronine were generously supplied by Smith, Kline & French Laboratories, Philadelphia, Pa.

that he felt "normal." After three weeks on this regimen, during which the basal metabolic rate was maintained at −5 to −10 per cent, all medication was omitted. One week later, a placebo (resembling the triiodothyronine tablet) was administered. The basal metabolic rate fell promptly on omission of *l*-triiodothyronine and three weeks later was −23 per cent; the serum cholesterol level rose to 242 mg. per 100 ml. The clinical change

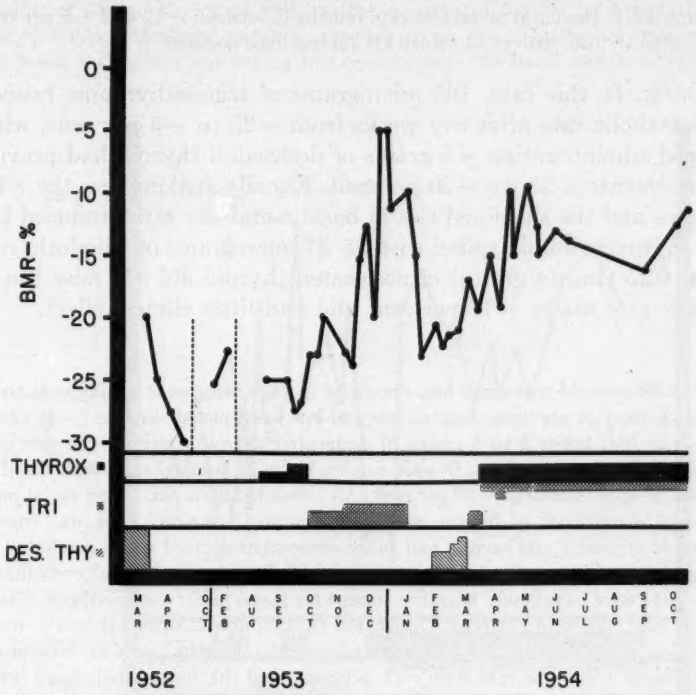

FIG. 1. The basal metabolic rate in Case I—R.B. (*see* case report for description). In all illustrations, the following abbreviations have been used: "THYROX" refers to *l*-thyroxine; "TRI" refers to *l*-triiodothyronine, and "DES. THY" refers to desiccated thyroid. The reference blocks are 0.1 mg., 25–35 micrograms and 0.065 Gm. (1 grain), respectively.

induced by the omission of triiodothyronine and the substitution of placebo medication was striking. The patient complained of severe lethargy, fatigue and puffiness of the eyes. At this time, a dose of 2 grains of desiccated thyroid was administered daily for fourteen days and 3 grains for an additional seven days, without effect on the clinical condition or basal metabolic rate. Four grains of desiccated thyroid for an additional seven days induced only a slight rise in the basal metabolic rate, from −21 to −17 per cent. Following omission of the desiccated thyroid, 70 micrograms of *l*-triiodothyronine for fourteen days failed to induce a further increase in the basal metabolic rate. For two weeks thereafter, a dose of 0.2 mg. of *l*-thyroxine was administered in combination with 35 micrograms of *l*-triiodothyronine. The basal metabolic rate began to rise. An additional 35

micrograms of *l*-triiodothyronine (*i.e.*, 70 micrograms of triiodothyronine and 0.2 mg. of thyroxine) for eight days was associated with a further increase in the basal metabolic rate. The patient complained of insomnia, nervousness, weakness, sweating, and increased appetite. The dose of *l*-triiodothyronine was reduced to 35 micrograms. The basal metabolic rate remained elevated, but the symptoms of thyroid toxicity subsided and the patient felt very well. On 25–35 micrograms of *l*-triiodothyronine and 0.2 mg. of *l*-thyroxine daily, the basal metabolic rate remained between −12 and −5 per cent for seven months and the patient sustained his clinical improvement.

Comment. In this case, 105 micrograms of triiodothyronine raised the basal metabolic rate after five weeks from −25 to −5 per cent, whereas prolonged administration of 5 grains of desiccated thyroid had previously failed to elevate it above −20 per cent. Equally striking was the relief of symptoms and the sustained rise in basal metabolic rate produced by 0.2 mg. of thyroxine administered with 25–35 micrograms of triiodothyronine, whereas 0.25 Gm. (4 grains) of desiccated thyroid did not raise the basal metabolic rate above −17 per cent and had little clinical effect.

Case II

W.G., a 38-year-old male, was first examined in 1944 because of aching in both knees. He gave a history of previous sluggishness and low basal metabolic rate (−40 per cent), for which he had taken 2 to 4 grains of desiccated thyroid daily for the previous ten years. Four of his maternal aunts were known to be hypometabolic, with basal metabolic rates of approximately −20 per cent. All presented skin pallor and facial puffiness and several complained of fatigue and aching joints; however, none was considered hypothyroid clinically and several had taken desiccated thyroid without relief of symptoms and without change in basal metabolic rate. Results of physical examination of W.G. in 1944 were completely negative, except for facial pallor and pastiness. The basal metabolic rate was −19 per cent. Desiccated thyroid was omitted. Over the course of the next ten years, the patient was seen infrequently, but had similar complaints. In 1945, the basal metabolic rate was −19 per cent, and the serum cholesterol level was 245 mg. per 100 ml. In 1952, the basal metabolic rate was −21 per cent, and the serum protein-bound iodine level was 6 micrograms per 100 ml. Examinations of blood and urine revealed nothing abnormal; the electrocardiogram showed a sinus rhythm, and a normal PR interval, QRS voltage and width. In July 1953, on routine examination, the patient described himself as feeling "quite normal." On physical examination, there was slight periorbital puffiness; the skin and hair had normal texture and the hands were cool and moist. The basal metabolic rate was −20 per cent, and the serum cholesterol level was 246 mg. per 100 ml.

The clinical data are presented in Figure 2. L-thyroxine, 0.1 mg. daily, was administered for thirty-eight days, 0.2 mg. for eighteen days, and 0.4 mg. for fourteen days. There was no significant change in the basal metabolic rate, serum cholesterol level or clinical condition. L-triiodothyronine, 70 micrograms administered daily for twenty-one days, was similarly without clear effect on the basal metabolic rate or serum cholesterol level; an increase of the dosage to 105 micrograms daily for the subsequent fifteen days was also without effect.

The substitution of 0.3 mg. of *l*-thyroxine daily for twenty-seven days immediately following this dose of triiodothyronine resulted in a rise of the basal metabolic rate to

−1 per cent. Following omission of *l*-thyroxine and substitution of 105 micrograms of *l*-triiodothyronine, the basal metabolic rate averaged −12 per cent for the next six weeks. When a placebo (open square in Fig. 2) was then substituted for *l*-triiodothyronine, the basal metabolic rate fell to −25 per cent and remained at that level during the ensuing twenty-four days while 0.3 mg. of *l*-thyroxine was administered daily. During this period, increased loginess, pallor and fatigability were noted. The addition of 35 micrograms of *l*-triiodothyronine daily to the regimen of 0.3 mg. of *l*-thyroxine was followed by a rise in the basal metabolic rate to −5 per cent. During the ensuing seven months, while the patient was taking this combination, the basal metabolic rate aver-

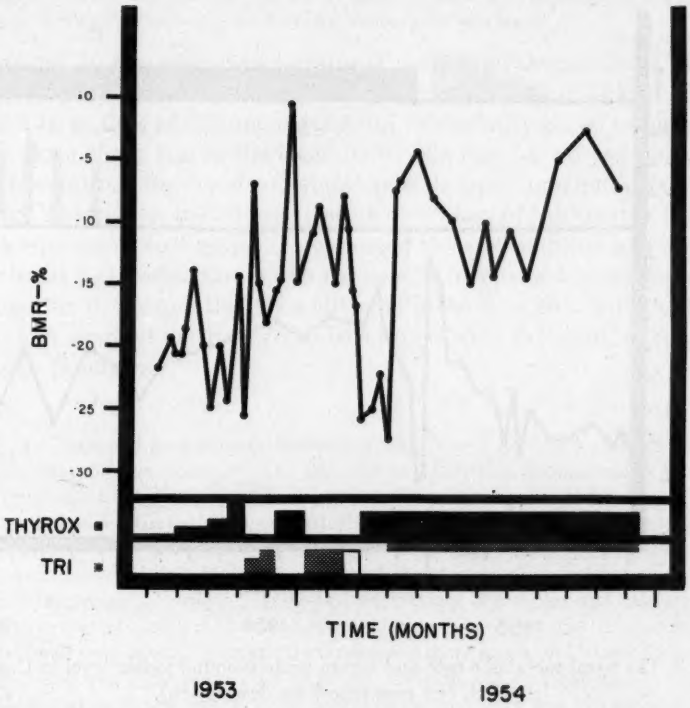

FIG. 2. The basal metabolic rate in Case II—W.G. (*see* case report for description).

aged −8 per cent (range, −2 to −15 per cent). Although he had initially considered himself "quite normal," he volunteered the statement that in retrospect there had been a definite sense of well being and increased vigor and alertness during this latter period.

Comment. In this case, 0.3 mg. of *l*-thyroxine daily immediately following fifteen days of 105 micrograms of *l*-triiodothyronine daily elevated the basal metabolic rate to −5 per cent, although 0.4 mg. of *l*-thyroxine alone and 70 micrograms of *l*-triiodothyronine alone had been ineffective. Sub-

sequently, 0.3 mg. of thyroxine plus 25–35 micrograms of triiodothyronine daily maintained the basal metabolic rate at −5 to −12 per cent and this metabolic change was accompanied by lasting clinical improvement.

Case III

H.H., a 46-year-old business man had been under medical observation for the previous twelve years. During this entire period, he had complained of easy fatigability, inability to lose weight, and periods of impotence. There were no other symptoms suggestive of hypothyroidism. There was no change in hair, skin or tongue. Two to 4 grains of desic-

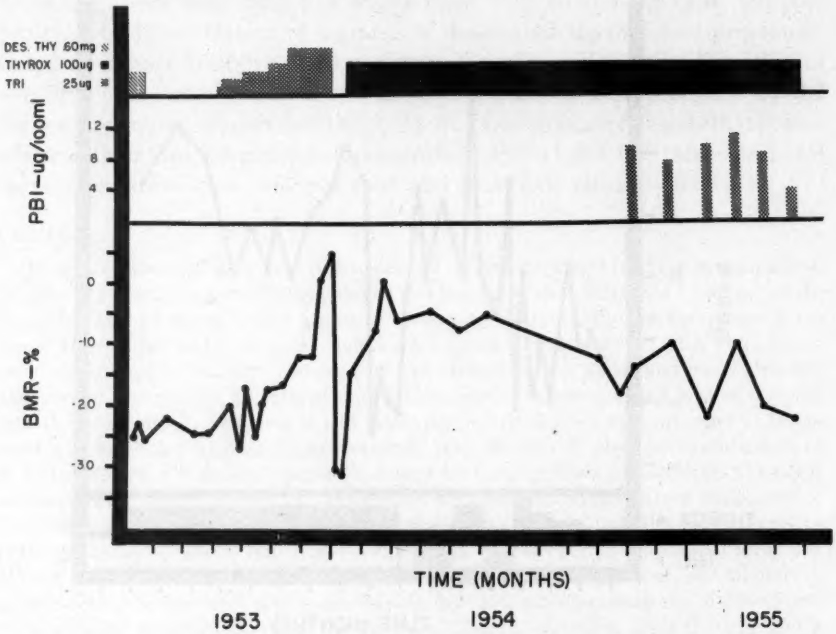

FIG. 3. The basal metabolic rate and serum protein-bound iodine level in Case III —H.H. (*see* case report for description).

cated thyroid had been taken daily for many years without relief of symptoms. During administration of 3 grains daily, the basal metabolic rate was −25 per cent. Findings on physical examination were negative, except for obesity and some facial pallor. All thyroid medication had been omitted for ten months before the present studies.

The data are presented in Figure 3. Seventy micrograms of *l*-triiodothyronine daily for two weeks had no clear effect on the basal metabolism; 105 micrograms daily for three weeks had only a slight effect, as did 140 micrograms daily; but 210 micrograms daily resulted in a gradual increase of basal metabolic rate and then a sudden further rise to +5 per cent. This was accompanied by restlessness and insomnia, but there was no palpitation, tremor, tachycardia or excessive perspiration. All medication was omitted

The basal metabolism fell to −30 per cent and the patient complained of lethargy, depression, weight gain, and sensitivity to the cold. A dose of 0.4 mg. of *l*-thyroxine daily was then administered. The basal metabolic rate rose rapidly within a week and during the next four weeks increased to about −5 per cent, where it remained for the next four to six months. The patient noted increased energy, improvement in mood, and decreased sensitivity to the cold. During the ensuing fifteen months, he was maintained on 0.4 mg. of *l*-thyroxine daily. The serum protein-bound iodine level varied from 7.7 to 11.1 micrograms per 100 ml. However, during the last eight months of this regimen, the basal metabolic rate decreased gradually and reached a level of −22 per cent. At this time, the serum protein-bound iodine concentration fell abruptly to 4.1 micrograms per 100 ml. Concomitantly, the patient noted a distinct increase in sensitivity to the cold and some gain in weight. There was no decrease in energy or alertness.

Comment. In this case, 2 to 4 grains of desiccated thyroid daily failed to elevate the basal metabolic rate above −25 per cent, but the administration of a large dose of 210 micrograms of *l*-triiodothyronine induced after four weeks a sharp rise in the basal metabolic rate to +5 per cent. When this was omitted, the basal metabolic rate dropped precipitously to −30 per cent. Thereafter, the administration of 0.4 mg. of *l*-thyroxine (approximately equivalent to 4 grains of desiccated thyroid) induced a gradual rise in the basal metabolic rate to −5 per cent, a level which persisted for the ensuing four to six months. Of additional interest in this patient was the subsequent gradual decline of the basal metabolic rate despite continued thyroxine therapy.

Case IV

H.Z., a 47-year-old male school teacher had complained for many years of headache, weakness, easy fatigue, sensitivity to the cold and bouts of despondency. Nine years before the present study, his basal metabolism was −22 per cent. A daily dosage of 1–2 grains of desiccated thyroid was prescribed, and the patient received this medication intermittently for the next eight years. There was no improvement in fatigue, lack of energy, and emotional irritability. It was noted that 1 grain of desiccated thyroid daily made him increasingly "jumpy." Testosterone, vitamin B complex and calcium pantothenate were also administered without effect. During the two months before our studies, no thyroid had been taken. On physical examination there was no evidence of myxedema, although there was slight periorbital puffiness; the skin was cool and moist. The basal metabolism was −25 per cent, and the serum cholesterol level was 175 mg. per 100 ml. Two determinations of serum protein-bound iodine averaged 5.5 micrograms per 100 ml. The 24-hour thyroidal uptake of a tracer dose of I^{131} was 32 per cent. Fifteen per cent of the circulating I^{131} was protein-precipitable at the end of twenty-four hours. When a mixture of the patient's plasma and I^{131} labelled thyroxine or triiodothyronine was incubated with a rat diaphragm, the diaphragm hormonal uptake was in the range of the uptake in other euthyroid persons (13). Similarly, when the patient's blood was incubated with I^{131}-labelled triiodothyronine, the uptake of radioactivity by the red blood cells was in a euthyroid range (15.7 per cent).

The data are presented in Figure 4. The administration of 0.2 mg. of *l*-thyroxine daily for one month and 0.3 mg. daily for an additional month was followed by a moderate rise in basal metabolism to approximately −20 and −15 per cent, respectively. The

serum protein-bound iodine level rose and after one week averaged 11.1 micrograms per 100 ml. (a value usually associated with thyrotoxicosis). This was accompanied by some improvement of the clinical state, in that there was a decrease in cold sensitivity and fatigue. For the following five weeks, 25 micrograms of *l*-triiodothyronine and 0.2 mg. of *l*-thyroxine were administered daily. For the first three weeks, there was no clear alteration of the metabolic rate; interestingly, the serum protein-bound iodine level was somewhat lower and averaged only 8.5 micrograms per 100 ml. Thereafter, the basal meta-

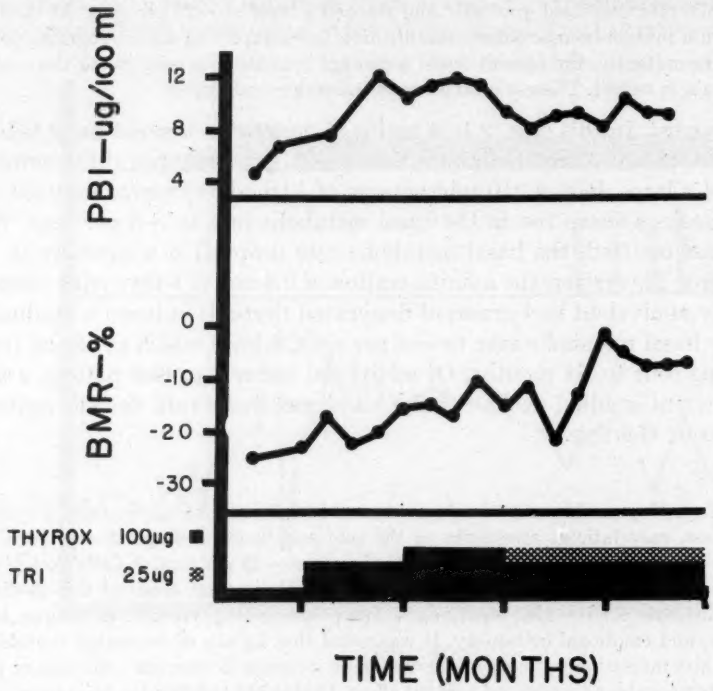

FIG. 4. The basal metabolic rate and serum protein-bound iodine level in Case IV—H.Z. (*see* case report for description).

bolic rate rose strikingly and for the next three weeks averaged −5 per cent. Further clinical improvement was noted, although irritability and emotional lability continued.

Comment. In this case, there was a moderate response to 0.3 mg. of *l*-thyroxine daily. It was notable that the basal metabolic rate rose to only −15 per cent, although the serum protein-bound iodine concentration was in the range usually found in hyperthyroidism. However, the administration of a combination of only 0.2 mg. of *l*-thyroxine and 25 micrograms of *l*-triiodothyronine daily resulted in a further rise in basal metabolism to −7 per cent, although the serum protein-bound iodine concentration was somewhat lower than before the administration of triiodothyronine.

DISCUSSION

The 4 patients described in detail are examples of non-myxedematous hypometabolism. The conclusion that such patients are not myxedematous rests on the absence of the usual clinical characteristics of myxedema, on normality of some parameters of thyroid function other than the basal metabolism, and on lack of response to moderate doses of desiccated thyroid or *l*-thyroxine. In this group, the 24-hour thyroidal uptake of a tracer dose of I^{131}, the serum protein-bound iodine level, and the serum cholesterol level were within normal limits in each case. However, the basal metabolism ranged from −20 to −25 per cent and the patients complained of lethargy, fatigue, irritability, and sensitivity to cold. Each had been treated with desiccated thyroid intermittently for many years without relief, and in 1 patient (Case I) 5 grains of desiccated thyroid daily had resulted in nervousness, palpitation and tachycardia without elevation of the basal metabolism above −20 per cent.

It is of considerable interest, therefore, that the basal metabolism in these euthyroid hypometabolic patients was clearly elevated by the oral administration of *l*-triiodothyronine and by combinations of triiodothyronine and *l*-thyroxine. Moreover, striking clinical improvement accompanied the rise in basal metabolism during triiodothyronine therapy. In considering the data, it is important to recall that other studies in man (14, 15) have shown *l*-triiodothyronine to be three to four times as active metabolically as *l*-thyroxine, and 0.1 mg. of *l*-thyroxine has been shown to be roughly equivalent to .065 Gm. (1 grain) of desiccated thyroid. On the basis of such data, one can consider 105 micrograms of *l*-triiodothyronine as the approximate metabolic equivalent of 3 to 4 grains of desiccated thyroid.

Case I illustrates the potency of triiodothyronine when desiccated thyroid had been ineffective. A dose of 105 micrograms of triiodothyronine daily raised the basal metabolic rate from −25 to −5 per cent, whereas 5 grains of desiccated thyroid had previously failed to elevate it above −20 per cent.

Cases I, II and IV demonstrate that the administration of a combination of triiodothyronine and thyroxine may be more effective than either alone. Thus, in Case I, 0.25 Gm. (4 grains) of desiccated thyroid daily did not raise the basal metabolic rate above −17 per cent and had little clinical effect; on the other hand 0.2 mg. of *l*-thyroxine daily administered simultaneously with 25–35 micrograms of *l*-triiodothyronine raised the metabolism to −12 per cent and resulted in relief of the symptoms of hypometabolism lasting seven months to date.

In Case II, 0.4 mg. of *l*-thyroxine daily failed to elevate the basal metabolism above approximately −20 per cent and 70 micrograms daily of triiodothyronine alone was likewise ineffective. However, 0.3 mg. of *l*-

thyroxine plus 25–35 micrograms of *l*-triiodothyronine daily maintained the basal metabolism at −5 to −12 per cent.

In Case IV, 0.3 mg. of *l*-thyroxine daily induced only a moderate rise in the basal metabolic rate from −25 to −15 per cent. On the other hand, 0.2 mg. of *l*-thyroxine combined with 25 micrograms of *l*-triiodothyronine daily elevated the basal metabolic rate to −5 per cent.

Finally, the data in Cases II and III provide evidence that a previously ineffective dose of thyroxine may raise the metabolic level when administered immediately after a large dose of triiodothyronine. In Case II, the administration of 0.4 mg. of *l*-thyroxine daily caused no significant change in the basal metabolic rate or clinical condition. However, 0.3 mg. of *l*-thyroxine immediately following fifteen days' administration of 105 micrograms of *l*-triiodothyronine daily resulted in a rise of the basal metabolic rate to −1 per cent.

In Case III, 2 to 4 grains of desiccated thyroid daily had failed to elevate the basal metabolic rate above −25 per cent, but the administration of a large daily dose of 210 micrograms of *l*-triiodothyronine induced, after a period of four weeks, a sharp rise in the basal metabolic rate to +5 per cent. When this was omitted, the basal metabolic rate dropped precipitously to −30 per cent. Thereafter, the daily administration of 0.4 mg. of *l*-thyroxine (approximately equivalent to 0.25 Gm. (4 grains) of desiccated thyroid) induced a gradual rise in the basal metabolic rate to −5 per cent, a level which persisted for the ensuing four to six months. It is of interest that during the last eight months, despite continuation of a previously effective dose of *l*-thyroxine, there was a gradual decline of the basal metabolic rate to a level of −22 per cent.

Several explanations were considered for the therapeutic results in these four cases. These included: 1) A defect in the absorption of thyroxine or desiccated thyroid from the gastrointestinal tract; in contrast, triiodothyronine might be more readily absorbed. Consistent with malabsorption would be the gradual fall of the basal metabolic rate in Case III accompanied by a drop in serum protein-bound iodine concentration, despite continued administration of *l*-thyroxine. However, this would not explain the spontaneous occurrence of the syndrome. Moreover, studies by others have shown a diminished response even to intravenous thyroxine in such cases. 2) Peripheral insensitivity to thyroxine, because of: (a) A defect in the transformation of thyroxine to a more active form. (b) Impaired permeability of the tissues of such patients to thyroxine but not to triiodothyronine. (Studies in our laboratory have indicated greater permeability of human red blood cells to triiodothyronine than to thyroxine. Investigations of possible abnormalities in plasma transport mechanisms and tissue permeability to thyroid hormones in such patients are now in progress.)

(c) A deficiency of triiodothyronine. This substance may be necessary for the optimal metabolism of thyroxine. The observed effectiveness of a combination of triiodothyronine and thyroxine (Cases I, II and IV) or of thyroxine immediately after prior dosage of triiodothyronine (Cases II and III) is consistent with this hypothesis. If there were a block in the metabolism of thyroxine (*i.e.*, failure to transfer it across cellular membranes or to convert it to an active form), one would anticipate a rise in the serum protein-bound iodine level during thyroxine therapy. This was indeed observed in Cases III and IV. One might also anticipate a drop in the level of serum protein-bound iodine when triiodothyronine was combined with thyroxine (16). It is of interest, therefore, that in Case IV a suggestive drop in the concentration of serum protein-bound iodine accompanied the rise in the basal metabolic rate when a daily dose of 0.2 mg. of *l*-thyroxine was administered in combination with 25 micrograms of triiodothyronine, compared to the level when it was administered alone.

SUMMARY

1. The clinical and laboratory characteristics of "euthyroid hypometabolism" have been reviewed. Such patients complain of lethargy, easy fatigue, nervousness, irritability, sensitivity to cold, headache, musculoskeletal pain, diminished sexual potency, and menstrual irregularity. The basal metabolism is depressed below −20 per cent, although the thyroidal I^{131} uptake and turnover, and the levels of serum protein-bound iodine and serum cholesterol are within normal limits. In contrast to the results in true hypothyroidism, the administration of moderate doses of desiccated thyroid often fails to elevate the metabolic rate or result in sustained clinical improvement.

2. Four cases of this sydrome have been presented and the response to triiodothyronine and to combinations of triiodothyronine and thyroxine have been described in detail. Each of these patients had previously received desiccated thyroid, often to the point of toxicity, without sustained clinical benefit. Nevertheless, the basal metabolic rate was clearly elevated following the oral administration of triiodothyronine, alone or with thyroxine, and striking clinical improvement accompanied the rise in the basal metabolic rate.

3. Several explanations for the observations are considered. Final choice among these must await additional experimental evidence.

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TRIIODOTHYRONINE IN THE SERUM OF PATIENTS TREATED WITH RADIOACTIVE IODINE*†

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THE presence of triiodothyronine in the serum of man was first demonstrated by Gross and Pitt-Rivers (1). In a previous report we described various radioiodinated amino acids, including triiodothyronine, which appeared in the sera of patients treated with radioactive iodine (2). Because labeled triiodothyronine was present in some of the samples of serum taken twenty-four hours after the administration of the I^{131}, the occurrence of iodinated compounds in the serum was explored further by the method of chromatographic fractionation. The following were investigated: 1) the frequency of occurrence of triiodothyronine in both Graves' disease and hyperfunctioning adenomatous goiter, 2) whether triiodothyronine is present in patients with normal functioning thyroid tissue, 3) the earliest time at which the compounds, especially triiodothyronine, are demonstrable in the serum, 4) whether radiation effect could explain the presence of the compounds by the time they first became detectable, and 5) the relationships between the circulating levels of thyroxine and triiodothyronine.

METHODS

Serial samples of serum from a total of 52 patients were studied by chromatographic fractionation. A series of fractionations was made for each of 39 patients with a clinical diagnosis of Graves' disease, 2 patients with hyperfunctioning thyroid adenoma, 4 patients with small remnants of

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thyroid tissue following nearly complete thyroidectomy for cancer, and 7 euthyroid patients with heart disease (Table 1). For every patient the series began within forty-eight hours of the administration of the I^{131}. An average of 7 samples, taken at intervals of a few days, were fractionated for each case. For 27 of the patients one or more fractionations were made on serum obtained less than twenty-four hours after the administration of the radioactive iodine.

The chromatograms were made from butanol extracts of serum by the method previously described (2). The paper strips were developed in a descending fashion, using a butanol-dioxane-ammonia solvent. Counting of the ¼-inch segments of the paper under a mica-window Geiger-Müller tube permitted the resolution of the peaks representing the various labeled

TABLE 1

Diagnosis	No. of patients	
	Total	With triiodothyronine in serum
Graves' disease	39	22
Toxic nodular goiter	2	1
Cancer; small remnants of thyroid	4	2
Euthyroid, with heart disease	7	2
Totals	*52*	*27*

compounds. Carriers of these compounds were usually added to lend assurance to the identification of the labeled compounds from the serum. No compound was considered to be present in significant amount unless three segments of paper in its area had a counting rate at least twice that of the background. A semi-quantitative estimate of the compounds present in the chromatogram was made by calculating the areas under the peaks.

The method of extraction permitted the recovery of 70 to 80 per cent of labeled iodide, thyroxine, triiodothyronine, and monoiodotyrosine added to serum. Only 50 per cent of added radioative diiodotyrosine was recovered, however. Thyroglobulin was not recovered by the extraction. Chromatographically pure radioactive iodide was added to serum in control experiments made to exclude interchange between iodide and organically bound iodine. Extraction and fractionation of this mixture produced only a single peak with a localization identical to that of carrier iodide.

RESULTS

Significant amounts of triiodothyronine were found in the sera from 22 of the 39 patients with Graves' disease (Fig. 1). Triiodothyronine represented between 2 and 14 per cent of the counts recorded from the chromatograms of these patients. Its concentration in the serum ranged from .007 to .213 per cent of the dose of I^{131} per liter in patients with Graves' disease. These concentrations are higher than those found in euthyroid patients, as will be described.

The recovery of triiodothyronine from the sera of patients with Graves'

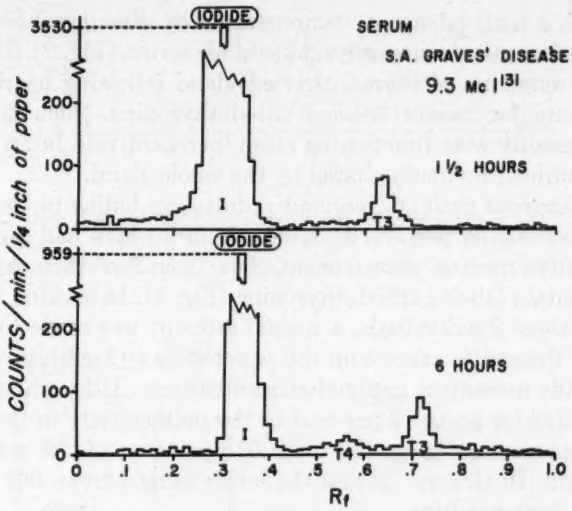

FIG. 1. Chromatographs of serum extracts from a patient with Graves' disease. Triiodothyronine (*T3*) was present in the 1½-hour specimen, whereas thyroxine (*T4*) first was detected in the 6-hour specimen. The ovals labeled iodide represent the location of carrier.

disease was related to the degree of toxicity as judged clinically, and also to the ratio of organic I^{131} to iodide I^{131} in the serum at twenty-four hours. Among 10 patients prejudged clinically to have severe thyrotoxicosis, 9 showed triiodothyronine, whereas this compound was present in a smaller proportion of moderately and mildly thyrotoxic patients (Table 2). Those patients with the most rapid conversion of iodide to organically bound iodine showed triiodothyronine most often, and those with slow conversion showed it less often (Table 3).

Triiodothyronine was detected in the sera of patients with hyperfunctioning thyroid tissue occurring for reasons other than Graves' disease. A

TABLE 2

Clinical severity of Graves' disease	No. of patients	
	Total	With triiodothyronine in serum
Mild	14	5
Moderate	15	9
Marked	10	9

patient with a toxic adenoma, demonstrated by directional counting, had significant amounts of triiodothyronine in his serum (Fig. 2). Two patients with small remnants of normal thyroid gland following nearly complete thyroidectomy for cancer showed triiodothyronine. Such thyroid remnants presumably were functioning at an increased rate in an attempt to carry the burden previously shared by the whole gland.

Seven euthyroid patients received radioactive iodine in the treatment of intractable angina pectoris or cardiac failure which had not responded to conservative medical management. Sera from 2 of these patients were found to contain labeled triiodothyronine (Fig. 3). In making the chromatograms of these 2 individuals, a special attempt was made to place large amounts of the serum extract on the paper strip to facilitate the recovery of compounds present in minimal concentrations. Although triiodothyronine accounted for up to 12 per cent of the radioactivity in the chromatogram, this percentage indicated only .010 per cent of the total dose per liter of serum. In Graves' disease the levels ranged from .007 to .213 per cent of the dose per liter.

Triiodothyronine was detected in the serum as early as one hour following the administration of radioactive iodine. It made its initial appearance

TABLE 3

Conversion ratio* (per cent)	No. of patients	
	Total	With triiodothyronine in serum
0–19	10	4
20–59	11	2
60–100	15	14

* $\frac{\text{Serum organic } I^{131}}{\text{Serum total } I^{131}}$ at twenty-four hours after the administration of the dose.

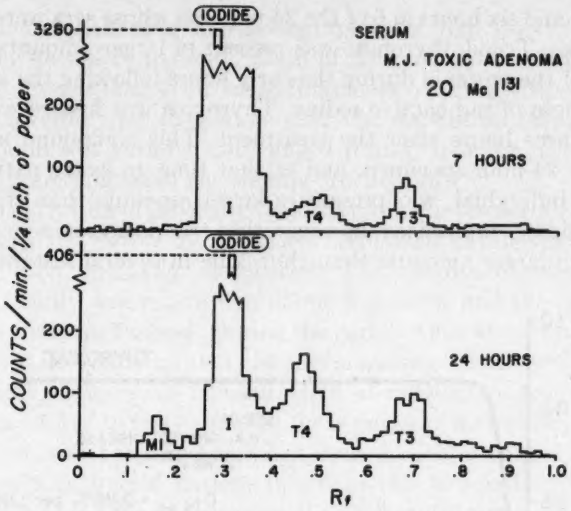

FIG. 2. The chromatographic fractionation of serum from a patient with toxic nodular goiter. The peaks represent monoiodotyrosine (*M*1), iodide (*I*), thyroxine (*T*4) and triiodothyronine (*T*3) in order of distance of travel from the place of application.

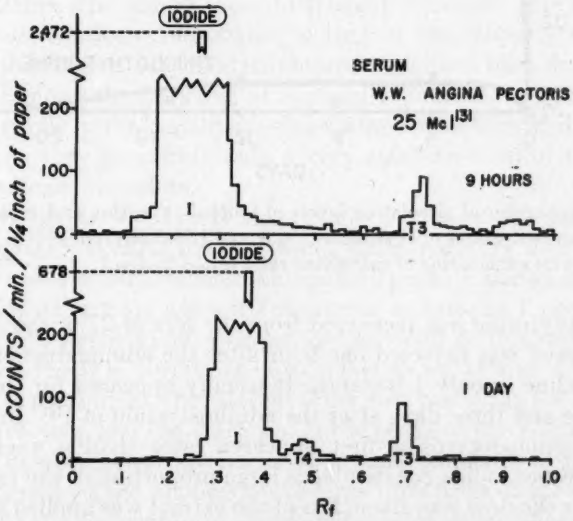

FIG. 3. Two chromatographs of the radioiodinated compounds in the serum of a euthyroid patient. Triiodothyronine (*T*3) appeared earlier and in larger amounts than thyroxine (*T*4).

between one and six hours in 6 of the 24 patients whose sera were examined at these times. Triiodothyronine was present in larger amounts than thyroxine in 5 of the patients during the early hours following the administration of the dose of radioactive iodine. Thyroxine was first recovered from the serum three hours after the treatment. This compound always was found in the 24-hour specimen, and at that time, in every patient except 1 euthyroid individual, was present in larger amounts than triiodothyronine. It should be emphasized, however, that triiodothyronine was detected earlier and in larger amounts than thyroxine in several instances.

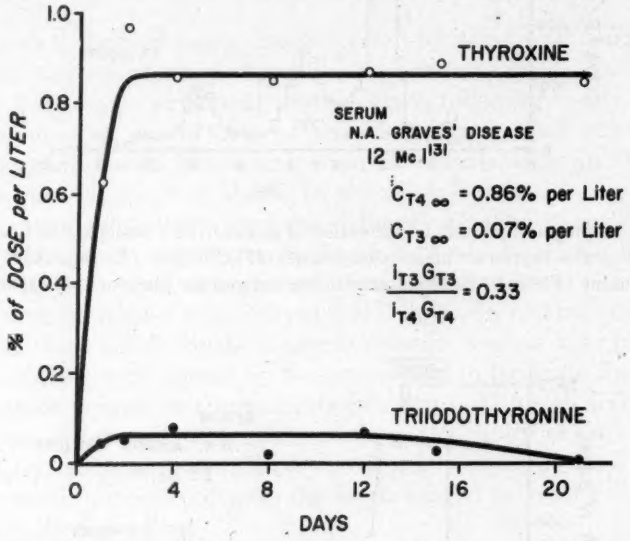

FIG. 4. Comparison of circulating levels of labeled thyroxine and triiodothyronine. The plateau concentrations of thyroxine ($C_{T4\infty}$) and triiodothyronine ($C_{T3\infty}$) are shown. (*See* discussion for explanation of calculated ratio $i_{T3}G_{T3}/i_{T4}G_{T4}$.)

Monoiodotyrosine was recovered from the sera of 27 of the 52 patients. This compound was detected one hour after the administration of the radioactive iodine in only 1 instance. It usually appeared for the first time between one and three days after the administration of I^{131}. In 6 patients, however, monoiodotyrosine first appeared later than a week following treatment. Since iodide constituted a large proportion of the radioactivity shortly after the dose was given, less of the extract was applied to the paper and monoiodotyrosine may have been missed until the iodide decreased. Monoiodotyrosine was found in all groups of patients described in this paper, including those who were euthyroid.

A compound behaving chromatographically like diiodotyrosine was found in the sera of 11 patients. Eight of these received radioactive iodine for Graves' disease, and 3 for small fragments of thyroid tissue remaining after thyroidectomy for thyroid cancer. The time of initial appearance of this compound was variable and ranged from four hours to thirteen days after the administration of the therapeutic dose of I^{131}.

The concentration of labeled triiodothyronine in the serum was greatest at about three days after the treatment, remained at this value for several days, and then gradually diminished. The maximum concentration of thyroxine usually was reached in about five days, and the concentration behaved in the same fashion. During the period when the serum levels were maintained at the plateau value, the concentration of radioactive thyroxine averaged twelve times the concentration of radioactive triiodothyronine, with a range of five to forty times in those patients with sufficient amounts of triiodothyronine to make a satisfactory comparison (Fig. 4). The serum from the only euthyroid patient in whom this comparison was possible contained ten times more thyroxine than triiodothyronine.

DISCUSSION

Triiodothyronine was identified in the sera of only half of the patients. Those individuals with triiodothyronine showed it in several consecutive chromatograms. The sera of those with negative results were studied by a series of fractionations comparable to that in the subjects with positive results. Failures to detect triiodothyronine may have been due to biologic differences among the patients. It is equally possible, however, that the failures were due to the inability of this method to detect the labeled compounds when they constitute only a very small fraction of the total circulating radioactive iodine.

Triiodothyronine was barely detectable in spite of the large amounts of I^{131} administered. Small doses would make recovery even less likely. Under favorable circumstances the method permits the identification of labeled triiodothyronine when it constitutes as little as 1 per cent of the circulating I^{131}. Recovery of a percentage as small as this was not always possible, as a result of variations in such factors as the size of the dose administered to the patient, the fraction of the dose present in the serum available for extraction, and the sharpness of the peaks on the chromatographic strip after development. Specimens with small amounts of radioactivity sometimes required the application of large quantities of the extract, and since these extracts contained an abundance of other substances, poor separation of the peaks occasionally resulted. The time required for processing the material from multiple specimens introduced a problem of physical decay which hampered the detection of minute amounts of these

compounds. To make the identification certain, no peak was accepted unless it was composed of at least 3 consecutive segments which had a counting rate twice that of background. This criterion eliminated from consideration a number of peaks which probably represented small amounts of triiodothyronine.

Triiodothyronine was most frequently detectable in the sera of patients who were severely thyrotoxic and who had high conversion ratios. The thyroid gland is depleted of its iodine stores in thyrotoxicosis (4). In iodine deficiency the I^{131} administered will constitute a greater proportion of the iodine available for synthesis. This will result in an increased amount of labeled triiodothyronine relative to the total amount of this compound, and may explain why triiodothyronine was detected more frequently in the patients with the most severe thyrotoxicosis.

Small but significant amounts of triiodothyronine were found in the sera of 2 patients with normally functioning thyroids. This confirmed the results of Gross and Pitt-Rivers (1). Although the ratio of labeled triiodothyronine to the total radioactivity on the chromatograms of euthyroid patients was the same as on those of hyperthyroid individuals, the concentration of this compound, expressed in per cent of the dose per liter, was considerably lower than in hyperthyroidism. It must be emphasized that no conclusions concerning the differences between the concentration of unlabeled triiodothyronine in the two types of patients can be reached from the measurement of labeled compounds alone. The low concentration of labeled triiodothyronine in normal subjects may be explained either by a decreased amount of unlabeled compound with the same ratio of labeled to unlabeled compound (specific activity), or a decrease in the specific activity with the same total amount. Probably both factors contributed to the observed difference.

When therapeutic amounts of radioactive iodine are used to label the compounds in the serum, there is always a possibility that the results are changed by the effects of the radiation. The prompt appearance of triiodothyronine in the serum after the administration of the I^{131} strongly suggests that its presence was not an effect of radiation. If it resulted from the radiation delivered in one hour, its concentration would be expected to increase markedly as further radiation effect occurred. This was not the case, and furthermore, triiodothyronine was recovered in instances in which the dose was not sufficient to control the hyperthyroidism. The evidence is not as clear concerning the relationship of monoiodotyrosine and diiodotyrosine to radiation damage. These compounds sometimes were present within four hours after the administration of the radioactive iodine, and their concentrations did not increase as further radiation damage occurred. In the few additional patients showing diiodotyrosine since

the report a year ago (2), the conclusion has not been confirmed that diiodotyrosine in the serum may be the result of radiation damage. These additional patients were not among those receiving the largest amounts of radiation of the gland, and some required an additional treatment to control the hyperthyroidism.

It has been suggested by Pitt-Rivers (3) that triiodothyronine may be a product of the peripheral deiodination of thyroxine. She has recovered labeled triiodothyronine from the serum of an athyreotic patient after the injection of labeled thyroxine. In some of the cases described here, the occurrence of labeled triiodothyronine in the serum sooner and in higher concentration than labeled thyroxine is evidence that triiodothyronine in the circulation is not a product of the peripheral deiodination of thyroxine. This is in agreement with the conclusion of Hogness and his coworkers (5), who found no interconversion between triiodothyronine and thyroxine injected into rats.

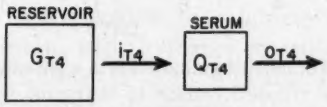

FIG. 5. Schematic representation of equilibration of a compound in the serum. Thyroxine ($T4$) is moving into the serum at a constant rate i_{T4} and out of the serum at a constant rate O_{T4}. The amount (G_{T4}) present in the reservoir is assumed constant, in order to predict changes in the amount of (Q_{T4}) in the circulation.

In those patients with significant amounts of triiodothyronine an attempt was made to calculate the relative rates of entry of triiodothyronine and thyroxine into the serum. Four basic quantities are considered: a reservoir containing an amount (G) of a compound, which is passing into the serum at a constant rate (i) and is moving out of the serum at a constant rate (o), and the quantity (Q) of the compound in the serum, which will vary with time (Fig. 5). The rate of change of the quantity (Q) in the serum is described by the equation $dQ/dt = iG - oQ$. If we postulate that the amount (G) of the compound in the reservoir is constant, this equation may be solved for the quantity (Q_t) in the serum at any time (t), and thus $Q_t = (i/o)G(1 - e^{-ot})$. When an asymptotic value of the compound in the serum is reached ($t = \infty$), then Q_∞ equals $(i/o)G$. The asymptotic concentration in the serum, C_∞, equals Q_∞/V, where V is the serum volume. If subscripts now are added to represent the various values pertaining to thyroxine ($T4$) and triiodothyronine ($T3$), then

$$\frac{C_{T3\infty}}{C_{T4\infty}} = \frac{o_{T4} i_{T3} G_{T3}}{o_{T3} i_{T4} G_{T4}}.$$

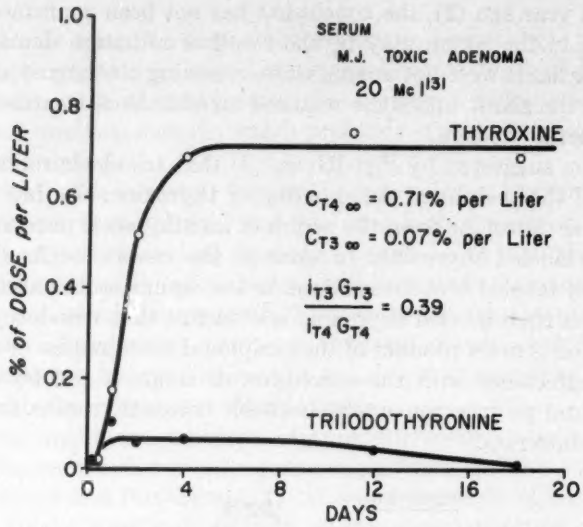

FIG. 6. Circulating levels of labeled amino acids in a patient with toxic nodular goiter. The ratio of the amount of triiodothyronine to thyroxine entering the serum ($i_{T3}G_{T3}/i_{T4}G_{T4}$) means that about 1 molecule of triiodothyronine entered the serum for every 3 molecules of thyroxine.

TABLE 4

Patient	$\frac{i_{T3}G_{T3}}{i_{T4}G_{T4}}$*	Comment
B.E.	.11	Moderate Graves' disease
B.H.	.12	Severe Graves' disease
W.J.	.18	Moderate Graves' disease
B.J.	.20	Severe Graves'; first treatment
H.C.	.22	Mild Graves' disease
S.A.	.30	Severe Graves' disease
N.A.	.33	Severe Graves' disease
S.R.	.36	Severe Graves'; second treatment
W.W.	.38	Angina pectoris; euthyroid
M.J.	.39	Toxic nodular goiter
B.J.	.40	Severe Graves'; second treatment
B.R.	.41	Cancer; small remnant normal gland
S.R.	.76	Severe Graves'; first treatment
J.J.	.92	Cancer; small remnant normal gland
P.J.	.95	Severe Graves' disease

* $\frac{i_{T3}G_{T3}}{i_{T4}G_{T4}} = \frac{4C_{T3\infty}}{C_{T4\infty}}$ = ratio of amounts of *T*3 and *T*4 entering the serum. (*See* text for explanation of symbols.)

The value of the ratio o_{T4}/o_{T3} is known, however, from the measurements of the disappearance of these compounds from the serum made by several investigators (6, 7), and has a value of about $\frac{1}{4}$. Thus

$$\frac{i_{T3}G_{T3}}{i_{T4}G_{T4}} = 4\frac{C_{T3\infty}}{C_{T4\infty}}.$$

The quantities $i_{T3}G_{T3}$ and $i_{T4}G_{T4}$ are the actual amounts of each compound entering the serum.

On the basis of this model, the concentrations of labeled triiodothyronine and thyroxine should rise in a logarithmic fashion to an asymptotic value. Two obvious difficulties occurred in fitting the data to the model. The concentrations of these two compounds often were found to decrease slightly after a maximum value was reached (Fig. 6). Moreover, the presence of triiodothyronine in the serum in greater amounts than thyroxine during the first hours can not be explained by the model. Despite these difficulties in some instances, it was possible to calculate the ratio between the amounts of triiodothyronine and thyroxine entering the serum. The average ratio was .33, with a range of .1 to .9 (Table 4), thus indicating that 1 molecule of triiodothyronine was entering the serum for every 3 molecules of thyroxine. The 1 euthyroid patient who had sufficient quantities of triiodothyronine to make this analysis possible had a ratio of .38, which coincides with the average value for the hyperthyroid patients.

It is not possible from studies of iodinated compounds in the serum to reach any definite conclusions about the origin of triiodothyronine. The appearance of triiodothyronine in the circulation before thyroxine is best explained, however, by considering that triiodothyronine is released from the thyroid gland and is not simply the result of the deiodination of thyroxine in the peripheral tissues.

SUMMARY

Labeled triiodothyronine has been identified by a method of chromatographic fractionation in the sera of 27 of 52 patients who were treated with radioactive iodine. It was recovered from 22 patients with Graves' disease, from 1 patient with a toxic nodular goiter, from 2 patients with remnants of thyroid tissue after nearly complete thyroidectomy for cancer, and from 2 euthyroid patients with heart disease. Triiodothyronine was detected as early as one hour after the administration of the I^{131}. The data suggest that triiodothyronine in the serum was not the result of radiation damage or of the peripheral deiodination of thyroxine, but was released from the thyroid gland into the circulation.

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DIAGNOSTIC ACCURACY OF SERUM PROTEIN-BOUND IODINE DETERMINATION IN THYROID DISEASE*

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IT IS generally acknowledged that the determination of the value for protein-bound iodine (PBI) in blood serum provides in most circumstances a direct quantitative estimation of the level of circulating thyroid hormone.

The practical usefulness of the measurement of serum protein-bound iodine was recognized soon after the technical difficulties with regard to its accurate determination had been overcome. Unfortunately, as is often the case with a new diagnostic test, protein-bound iodine was promptly put to clinical use despite a comparative paucity of well-documented experience describing the extent of its variation in health and disease or the diagnostic precision with which it can be applied to clinical problems.

Numerous papers on this subject have appeared previously (1–14). In many instances, however, conclusions have been drawn from the study of patients in whom the level of thyroid function was not fully characterized on the basis of data independent of the protein-bound iodine. The present study was undertaken because there appeared to be a need for more precise definition of the clinical potentialities of protein-bound iodine.

The plan of study employed has been to evaluate the level of serum protein-bound iodine observed in a substantial number of patients at the Mayo Clinic who, according to most rigorous diagnostic criteria exclusive of the test in question, were considered to be normal with regard to thyroid function. Comparison of the range of values so obtained with that of values obtained in different diseases of the thyroid gland defines the degree of overlap to be expected and delineates the usefulness of the test in the clinical evaluation of thyroid function.

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MATERIALS AND METHODS

Estimations of PBI were carried out in duplicate on 1-ml. samples of serum, the protein being precipitated with zinc sulfate and sodium hydroxide, according to the method of Somogyi (15). The precipitate was washed twice by centrifugation after thorough suspension in 10-ml. portions of distilled water and was transferred to 500-ml. digestion flasks with 25 ml. of 21N sulfuric acid. Digestion by chromic acid, subsequent distillation and determination of iodide in the distillate by its catalytic effect on the cerate-arsenite reaction followed the general procedure of Chaney (16), as adapted by Barker (17) and others, including us. The variability of the procedure in our hands was tested by frequent analysis of pooled serums containing different amounts of iodine. For example, the values obtained for total iodine in one such pool, when single samples were taken for analysis on ten separate days, ranged from 4.4 to 5.2 micrograms per 100 ml. of

TABLE 1. CASES EXCLUDED FROM STUDY

Reason for exclusion	No. of cases
Definitive diagnosis not established	132
Previous administration of iodized radiopaque dyes	51
Recent treatment with antithyroid drugs	32
Recent treatment with inorganic iodine	15
Recent treatment with desiccated thyroid	13
Recent radioiodine therapy	4
Previous subtotal thyroidectomy	8
Severe nephrosis	2
Cirrhosis of liver	2
Total	*259*

serum (mean, 4.81; standard deviation, 0.265). In another pool containing considerably more iodine, the values obtained on nine different days ranged from 15.6 to 17.0 micrograms per 100 ml. (mean, 16.2; standard deviation, 0.487).

Tests with radioactive iodine indicated that the over-all recovery from samples containing total amounts of iodine ranging from 0.04 to 0.10 microgram varies from 85 to 90 per cent. Loss was incurred primarily during distillation. In agreement with Taurog and Chaikoff (18), we noted that little if any loss of radioactivity occurs during digestion by chromic acid. Although Barker (17) suggested adding a correction of 10 per cent to account for failure of quantitative recovery, so many other sources of variability are present that we have preferred to record our results without correction.

We reviewed the records of 1,542 patients in whom serum PBI was measured between January 1, 1949 and December 31, 1951, inclusive. The cases were then separated into eight groups on the basis of all clinical and laboratory evidence available, exclusive of PBI. Such evidence included 1) history and physical examination, 2) laboratory data such as basal metabolic rate, level of plasma cholesterol and thyroidal accumulation of radioiodine, 3) clinical response to treatment, and 4) repeated follow-up observations. Cases in which such information was considered to be inconclusive were excluded from the study. In no instance was the value for PBI allowed to influence the final evaluation of the patient's thyroid function.

Also excluded from study were all cases in which the level of PBI might have been influenced by the ingestion of inorganic iodine, antithyroid drugs or desiccated thyroid, by the prior administration of iodine-containing radiopaque dyes or other iodine-containing drugs, by previous thyroidectomy, or by the presence of nephrosis or cirrhosis of the liver.

Two hundred and fifty-nine cases were excluded from the study for one or more of these reasons; these cases are listed in Table 1.

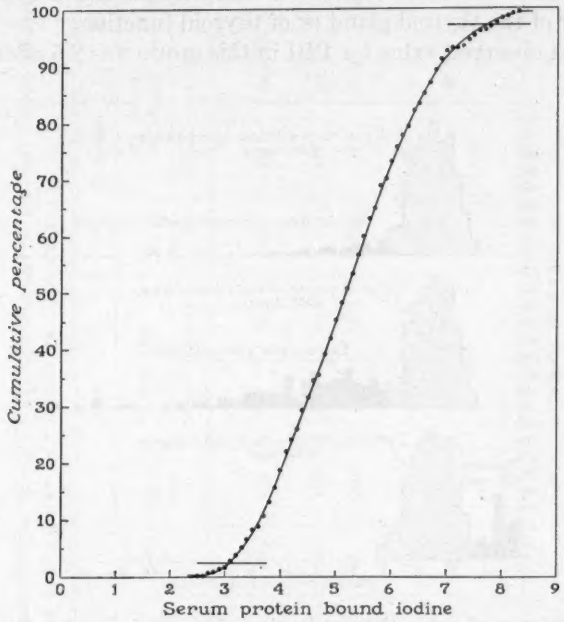

FIG. 1. Cumulative distribution curve of values for protein-bound iodine (μg. per 100 ml.) in 530 euthyroid persons without thyroid disease. Ninety-five per cent of values fall within the range defined by intercepts of this curve at the 2.5 per cent and 97.5 per cent levels.

In order to determine a range of values that would be expected to include 95 per cent of euthyroid persons without thyroid disease, a smoothed cumulative distribution curve (Fig. 1) was constructed from observed values for PBI in 530 such persons. The range selected was taken from the intercept of this curve at 2.5 and 97.5 per cent levels, respectively. As will be noted later, the range determined by this curve actually included 95.6 per cent of euthyroid persons but for purposes of practical comparison it is considered to be the 95 per cent range.

RESULTS

The distribution of the values for PBI observed in euthyroid, hyperthyroid and hypothyroid persons is shown in Figure 2. The numbers of

cases classified in each of the first six diagnostic categories, as well as the mean values for the basal metabolic rate, plasma cholesterol level and thyroidal accumulation of radioiodine, are listed in Table 2.

Group I: Euthyroid persons without thyroid disease. This group consisted of 530 patients examined routinely at the clinic for a variety of complaints and in whom the history, physical examination, laboratory studies (other than the level of PBI) or subsequent observations failed to disclose any abnormality of the thyroid gland or of thyroid function.

The lowest observed value for PBI in this group was 2.5 micrograms per

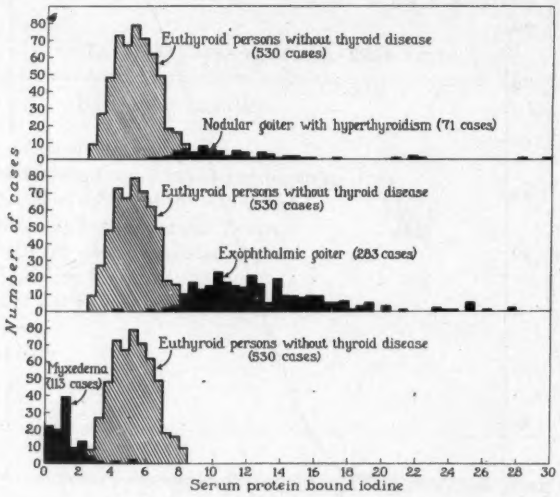
Euthyroid persons without thyroid disease (530 cases)
Nodular goiter with hyperthyroidism (71 cases)
Euthyroid persons without thyroid disease (530 cases)
Exophthalmic goiter (283 cases)
Euthyroid persons without thyroid disease (530 cases)
Myxedema (113 cases)
Number of cases
Serum protein bound iodine

FIG. 2. Histogram showing the distribution of values for protein-bound iodine (μg. per 100 ml.) in euthyroid, hyperthyroid and hypothyroid persons.

100 ml. of serum and the highest was 8.3; the mean value was 5.2 micrograms, with a standard deviation (S.D.) of 1.2 (Table 3). Of these euthyroid persons, 95.6 per cent had values for PBI that fell between 3.1 and 7.7 micrograms per 100 ml. of serum; 12 patients (2.3 per cent) had values below and 11 (2.1 per cent) had values above this range.

Group II: Nodular goiter without hyperthyroidism. This group included 136 patients with nodular goiter who were considered on the basis of history, physical examination, laboratory data and subsequent observations to be euthyroid.

The lowest observed value for PBI in this group was 3.2 micrograms per 100 ml. of serum and the highest was 8.4; the mean value was 5.4 micrograms, with an S.D. of 1.2 (Table 3). Of these 136 patients, 134 (98.5

TABLE 2. BASAL METABOLIC RATE, PLASMA CHOLESTEROL LEVEL AND THYROIDAL UPTAKE OF RADIOIODINE IN VARIOUS THYROID STATES

Diagnosis	No. of cases			Mean age, yrs.	BMR			Cholesterol			24-Hour uptake of I^{131}		
	Total	Male	Female		No. of tests	Rate (%)		No. of tests	Mg. per 100 ml. plasma		No. of tests	Per cent of dose	
						Mean	S.D.*		Mean	S.D.*		Mean	S.D.*
Group I: Euthyroid persons, without thyroid disease	530	192	338	46	458	+11	14.2	111	211	56.8	86	26.3	12.9
Group II: Nodular goiter without hyperthyroidism	136	30	106	55	126	+11	13.4	23	218	58.9	31	28.2	15.2
Group III: Exophthalmic goiter	283	87	196	48	280	+31	15.3	79	187	44.6	147	58.4	16.9
Group IV: Nodular goiter with hyperthyroidism	71	16	55	55	71	+27	14.8	13	163	34.9	28	37.3	23.3
Group V: Hypothyroidism	113	30	83	46	112	−21	9.2	92	327	88.8	14	6.2	6.9
Group VI: Low BMR without hypothyroidism	58	12	46	39	58	−20	3.9	44	229	64.1	—	—	—

* S.D. = standard deviation.

per cent) had values within the 95 per cent range for euthyroid persons without thyroid disease.

Group III: Exophthalmic goiter.[1] Patients who had exophthalmic goiter numbered 283. The lowest value for PBI in this group was 4.4 micrograms per 100 ml. of serum and the highest was 27.0; the mean value was 12.7 micrograms, with an S.D. of 4.0 (Table 3). Eight patients (2.8 per cent) had

TABLE 3. VALUES FOR PBI IN VARIOUS THYROID STATES

Diagnosis	No. of cases	PBI (μg. per 100 ml. serum)		Per cent within 95% range for Group I*
		Mean	Range	
Group I: Euthyroid persons without thyroid disease	530	5.2 (1.2)†	2.5– 8.3	—
Group II: Nodular goiter without hyperthyroidism	136	5.4 (1.2)	3.2– 8.4	98.5
Group III: Exophthalmic goiter	283	12.7 (4.0)	4.4–27.0	2.8
Group IV: Nodular goiter with hyperthyroidism	71	11.6 (4.5)	6.3–30.0	9.9
Group V: Hypothyroidism	113	1.3 (0.95)	0.0– 5.2	3.5
Group VI: Low BMR without hypothyroidism	58	4.9 (1.3)	2.6– 7.8	94.8

* This 95 per cent range = 3.1–7.7 μg. per 100 ml.

† Numbers in parentheses are the standard deviations.

values for PBI of less than 7.7 micrograms, the upper limit of the 95 per cent range for our group of euthyroid persons. Table 4 lists the initial value for PBI, the basal metabolic rate, the level of plasma cholesterol and the 24-hour thyroidal uptake of radioiodine, as well as the method and results of treatment, in each of these 8 patients.

[1] The term "exophthalmic goiter" as used here is considered synonymous with so-called toxic diffuse goiter or "Graves' disease," characterized by diffuse hypertrophy of thyroid follicle cells. Exophthalmos may or may not be present.

TABLE 4. EXOPHTHALMIC GOITER: CASES WITH PBI LESS THAN 7.7 μg. PER 100 ML. OF SERUM

Case	PBI	BMR (%)	Cholesterol (mg. per 100 ml. plasma)	24-Hour uptake of radioiodine (% of dose)	Treatment	Response	
						Clinical	BMR (%)
1	4.4	+34	197	62.2	Radioiodine	Excellent	+ 3
2	6.0	+24	—	48.3	Subtotal* thyroidectomy	Excellent	+ 1
3	7.0	+25	97	60.2	Radioiodine	Excellent	−10
4	7.0	+18	197	54.5	Lugol's	Good	+ 1
5	7.1	+22	177	67.4	Radioiodine	Excellent	− 9
6	7.2	+19	—	52.2	Lugol's	Good	+ 1
7	7.3	+39	140	37.8	Radioiodine	Excellent	−14
8	7.5	+27	127	—	Subtotal* thyroidectomy	Excellent	—

* Histologic diagnosis was diffuse parenchymatous hypertrophy.

Group IV: Nodular goiter with hyperthyroidism. In the 71 patients with nodular goiter considered to be hyperthyroid, the lowest value for PBI was 6.3 micrograms per 100 ml. of serum and the highest was 30.0; the mean value was 11.6 micrograms, with an S.D. of 4.5 (Table 3). Seven patients (9.9 per cent) had values for PBI less than 7.7 micrograms. Table 5 lists the initial value for PBI, the basal metabolic rate, the level of plas-

TABLE 5. NODULAR GOITER WITH HYPERTHYROIDISM:* CASES WITH PBI LESS THAN 7.7 μg. PER 100 ML. OF SERUM

Case	PBI	BMR (%)	24-Hour uptake of radioiodine (% of dose)	Response to treatment	
				Clinical	BMR (%)
9	6.3	+20	—	Excellent	+ 5
10	6.8	+10	71.7	Excellent	− 3
11	7.3	+25	56.5	Good	+ 2
12	7.4	+22	32.5	Excellent	− 5
13	7.5	+24	—	Excellent	− 7
14	7.6	+35	49.5	Excellent	+10
15	7.6	+44	34.9	Excellent	+ 5

* Treatment was subtotal thyroidectomy in all but Case 11 (radioiodine); in all surgical cases, histologic diagnosis was multiple adenomatous goiter.

ma cholesterol and the 24-hour thyroidal accumulation of radioiodine, as well as the method and results of treatment, in these 7 patients.

Group V: Hypothyroidism. This group was composed of 113 patients considered to be hypothyroid. Included are 63 instances of spontaneous myxedema, 34 instances of myxedema secondary to subtotal thyroidectomy and 16 instances in which hypothyroidism was secondary to radioiodine therapy for hyperthyroidism or cancer of the thyroid gland.

The values for PBI in this group ranged from zero to 5.2 micrograms per 100 ml. of serum; the mean value was 1.3 micrograms, with an S.D. of 0.95 (Table 3). Four patients (3.5 per cent) had values for PBI within the 95 per cent range for euthyroid persons. The values for PBI, the basal

TABLE 6. MYXEDEMA: CASES WITH PBI MORE THAN 3.1 μg. PER 100 ML. OF SERUM

Case	Type of myxedema	PBI	BMR (%)	Cholesterol (mg. per 100 ml. plasma)	Response to desiccated thyroid		
					Clinical	BMR (%)	Cholesterol (mg. per 100 ml. plasma)
16	Postoperative	3.3	−21	443	Excellent	+5	—
17	Postoperative	4.4	−21	353	Excellent	−3	155
18	Spontaneous	5.1	−26	300	Excellent	−9	187
19	Spontaneous	5.2	−17	405	Excellent	+3	167

metabolic rate and the level of plasma cholesterol in these 4 patients, as well as their response to the administration of desiccated thyroid substance, are listed in Table 6.

Group VI: Low basal metabolic rate without hypothyroidism. Included in this classification are patients who had basal metabolic rates less than −13 per cent[2] but in whom signs and symptoms of true myxedema were lacking and in whom administration of desiccated thyroid failed to result in the clinical changes that characteristically occur when this hormone is given to patients who have true myxedema.

In the 58 patients so classified, the lowest value for PBI was 2.6 micrograms per 100 ml. of serum and the highest was 7.8; the mean value was 4.9 micrograms, with an S.D. of 1.3 (Table 3). Of these 58 patients, 94.8 per cent had values for PBI in the range that includes 95 per cent of euthyroid persons.

[2] The data of Boothby and Sandiford (19) were used, in which the range that includes 95 per cent of euthyroid persons is from +13 per cent to −13 per cent.

Group VII: Anterior pituitary insufficiency. It is difficult in many cases of anterior pituitary insufficiency to assess the degree to which thyroid function has been impaired, because of the accompanying symptoms and signs of other end-organ deficiencies. However, 30 patients with varying degrees of anterior pituitary insufficiency were studied. Clinical evidence of hypothyroidism was striking in 18 of this group. It appeared likely that

TABLE 7. VALUES FOR PBI IN VARIOUS THYROID STATES

Diagnosis	No. of cases	PBI (μg. per 100 ml. serum)		Per cent within 95% range for euthyroid persons without thyroid disease*
		Mean	Range	
Group VII: Pituitary insufficiency	30	2.8	0.2– 5.4	46.6
Group VIII: Miscellaneous. Acute diffuse thyroiditis	13	8.5	5.4–13.2	38.5
Hashimoto's thyroiditis with myxedema	14	1.8	0.1– 4.4	14.3
Colloid goiter (euthyroid)	7	4.7	2.5– 7.3	85.7
Cancer of the thyroid (euthyroid)	13	4.9	2.8– 8.4	84.6
Drug-induced myxedema (propylthiouracil or KSCN)	15	0.6	0.0– 2.1	0.0

* This 95 per cent range = 3.1–7.7 μg. per 100 ml.

residual thyroid function was present in the remaining 12 patients, in whom clinical evidence of hypothyroidism was not so apparent. The lowest value for PBI in the group was 0.2 microgram per 100 ml. of serum and the highest was 5.4; the mean value was 2.8 micrograms (Table 7). Fourteen (46.6 per cent) of these 30 patients had values for PBI within the 95 per cent range for euthyroid persons.

Group VIII: Miscellaneous thyroid disorders. Included in this category are 62 patients who suffered from a variety of thyroid diseases (Table 7). Twenty of these patients were euthyroid and 29 were frankly hypothyroid. The remaining 13 patients, who had acute or subacute diffuse thyroiditis, exhibited various levels of thyroid function.

COMMENT

The values for PBI in the euthyroid, hyperthyroid and hypothyroid persons included in our study are in general agreement with the values previously published by others (Tables 8 and 9). Our data, however, do not support the statement of Starr (20, 21) that values for PBI less than 4 or more than 8 micrograms per 100 ml. of serum by definition indicate the existence of disordered thyroid function. Had such criteria been employed in our study, 91 patients in whom independent data indicated

TABLE 8. VALUES FOR PBI IN EUTHYROID PERSONS

Author	No. of cases	PBI (μg. per 100 ml. serum)		
		Mean	S.D.*	Range
Turner and associates (1)	40	6.3	—	3.5–10.4
Salter and associates (2)	21	5.7	1.0	4.0– 8.0
Riggs (5)	55	5.1	—	3.5– 7.5
Perry and Cosgrove (6)	34	5.9	1.3	4.0– 9.3
Kydd and associates (7)	83	5.3	1.0	3.8– 8.6
Starr and associates (8)	100	5.5	0.9	4.0– 8.5
Barker and associates (9)	68	5.1	1.0	3.4– 8.0
Tucker and Keys (10)	402	5.8	1.3	2.6–11.1
Hallman and associates (11)	37	5.4	1.08	3.2– 7.6
Sunderman and Sunderman (12)	65	5.0	1.0	2.9– 7.9
Zak and associates (13)	120	—	—	3.5–11.3
Winikoff (14)	106	5.1	—	2.7– 8.0
Blackburn and Power (this report)	530	5.2	1.2	2.5– 8.3

* Standard deviation.

normal thyroid function would have been classified as abnormal. Such a rigid biochemical definition of abnormality ignores the existence of a small range of values for PBI common to both euthyroid persons and those who have disordered thyroid function.

Our data, as well as those of others (1–9, 11–14), indicate that the occurrence of normal values for PBI in patients with abnormal thyroid function is unusual. Moreover, the data reported in this study indicate that in patients with disordered thyroid function the PBI is less likely to be normal than is either the basal metabolic rate or the uptake of radioiodine (Table 10). Shown in Table 10 is the proportion of hyperthyroid and hypothyroid patients in whom values for the basal metabolic rate, PBI and uptake of radioiodine were within the 95 per cent range for euthyroid persons. In making this comparison of diagnostic accuracy, we selected from the total number of hyperthyroid and hypothyroid patients only those on whom all three tests were performed.

TABLE 9. VALUES FOR PBI IN HYPERTHYROIDISM AND HYPOTHYROIDISM

Author	Hyperthyroidism			Hypothyroidism		
	No. of cases	PBI (μg. per 100 ml. serum)		No. of cases	PBI (μg. per 100 ml. serum)	
		Mean	Range		Mean	Range
Turner and associates (1)	20	15.9*	6.7–38.5	—	—	—
Winkler and associates (3, 4)	87	13.8	4.9–55.1	25	1.3	0.2–2.5
Kydd and associates (7)	206	—	7.1–48.2	93	—	0.0–3.0
Starr and associates (8)	208	12.3	3.5–25+	39	2.1	—
Sunderman and Sunderman (12)	56	—	6.5–29.0	15	—	0.4–3.4
Blackburn and Power (this report)	354†	12.1	4.4–30.0	113	1.3	0.0–5.2

* Calculated from Table 2 of Turner's group.

† Includes 283 cases of exophthalmic goiter and 71 cases of nodular goiter with hyperthyroidism.

The technic for determination of PBI has the advantage of eliminating the need for the patient's co-operation to the extent that is required for accurate determination of the basal metabolic rate. For this reason, it is extremely useful in the evaluation of thyroid function in patients whose anxiety and nervousness prevent accurate determination of the basal metabolic rate. It is equally useful in patients with hypertension, cardiac

TABLE 10. COMPARATIVE DIAGNOSTIC ACCURACY OF PBI, BMR AND UPTAKE OF RADIOIODINE

Diagnosis	No. of cases	Per cent within 95% range for euthyroid persons*		
		PBI	BMR	24-Hour uptake of radioiodine
Exophthalmic goiter	147	4.7	12.2	16.3
Nodular goiter with hyperthyroidism	28	11.1	22.2	57.1
Hypothyroidism	14	0	21.4	21.4

* These 95 per cent ranges for euthyroid persons without thyroid disease are: PBI = 3.1–7.7 μg. per 100 ml. serum; BMR = ±13 per cent; uptake of radioiodine = 11–46 per cent of dose (McConahey and associates (22)).

failure, parkinsonism, blood dyscrasias or other diseases sometimes associated with extrathyroidal hypermetabolism.

In cases of suspected hypothyroidism in which the basal metabolic rate is at an equivocal level, or for the separation of patients with true myxedema from euthyroid persons having basal metabolic rates below the generally accepted normal range, determination of the PBI level may provide decisive diagnostic information that no other test of thyroid function affords.

The measurement of PBI appears to be a reliable laboratory means for the detection of hyperthyroidism in a large proportion of patients with nodular goiter, a group in which the results of other tests of thyroid function are frequently inconclusive. In this condition, studies of thyroid function employing radioiodine have little specificity. The euthyroid goitrous patient frequently shows a thyroidal accumulation of radioiodine above the normal range, and many patients with toxic nodular goiter have a normal uptake of radioiodine (23). Furthermore, the presence of hypertension or cardiac failure in many patients with toxic nodular goiter frequently prevents accurate determination of the basal metabolic rate. In this study, the PBI provided a more accurate means for the detection of hyperthyroidism in these patients than did either the basal metabolic rate or the thyroidal accumulation of radioiodine.

Aside from the technical difficulty of its determination, the chief disadvantage of the use of PBI as a diagnostic test is the frequency with which previous administration of inorganic iodine, radiopaque iodine-containing dyes or other iodine-containing compounds renders its determination meaningless. This problem is illustrated by the fact that 66 of our total of 1,542 cases (4.3 per cent) had to be excluded for these reasons and that, in an indeterminate but probably large number of cases, the test was not attempted on this account.

The high degree of accuracy with which measurement of PBI delineates thyroid function indicates that it is a superior test in the clinical detection of abnormal function. However, difficult diagnostic problems in thyroid disease are frequently encountered, in which other laboratory tests of thyroid function are necessary. For this reason, we consider that the combined use of all tests of thyroid function in such cases provides more decisive information than does exclusive use of any single test.

SUMMARY AND CONCLUSIONS

A study has been made of the records of 1,542 patients at the Mayo Clinic in whom the level of protein-bound iodine (PBI) in the serum was determined. Thyroid function was determined in each patient on the basis of data other than the PBI.

Excluded from the study were 259 patients for whom insufficient evidence was available to permit accurate appraisal of thyroid function or because extraneous factors were present that might have affected the level of PBI.

The range of values for PBI and the mean values obtained in patients who had different diseases of the thyroid gland have been presented. The range of values that included 95 per cent of euthyroid persons without thyroid disease was also determined. The proportion of patients in the various diagnostic categories of thyroid disease who had values for PBI within this range was considered to be an index of the accuracy with which measurement of PBI delineates thyroid function.

The diagnostic accuracies of PBI, of the basal metabolic rate and of the uptake of radioiodine were compared. In this study, determination of the serum PBI level proved to be the most valuable single test in the clinical evaluation of thyroid function; it often provided decisive diagnostic information when the results of other tests were inconclusive. However, in the small proportion of patients with abnormal thyroid function who had values for PBI within the normal range, other tests of thyroid function often were unequivocally abnormal. Therefore, in difficult problems of thyroid disease, combined use of all tests of thyroid function may be necessary for accurate diagnosis.

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HISTOLOGY OF THE HUMAN HYPOPHYSIS IN THYROID DISEASE—HYPOTHYROIDISM, HYPERTHYROIDISM, AND CANCER*†

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RECENT experiments on laboratory animals (1–4) show that thyroid deficiency will induce hyperplasia of a specific cell type in the adenohypophysis, which is presumed to be the source of thyrotropic hormone (TSH). This paper is a study of the human hypophysis in thyroid deficiency, thyrotoxicosis and cancer of the thyroid, in an attempt to see if any particular cell can be linked with TSH production in man and what changes, if any, are induced by various therapeutic procedures.

MATERIAL AND METHODS

Differential counts were performed on all hypophyses which were stained by the periodic-acid Schiff reaction and an Orange G counterstain. This technique differentiates six cell types as follows:

1. *Normal basophils.* These are densely granulated, intensely Schiff positive cells (Figs. 1–6).

2. *Acidophils.* These are densely granulated, Schiff negative cells which stain brightly with Orange G (Figs. 4 and 6).

3. *Amphophils.* These are more sparsely granulated, weakly Schiff positive cells which may vary considerably in morphology, numbers of granules, and intensity of staining reaction. The cell boundaries are often indistinct and irregular, as opposed to the rounded, sharp outlines of basophils and acidophils. The nucleus is usually large and vesicular and may contain a prominent nucleolus. The cytoplasm may contain a few large,

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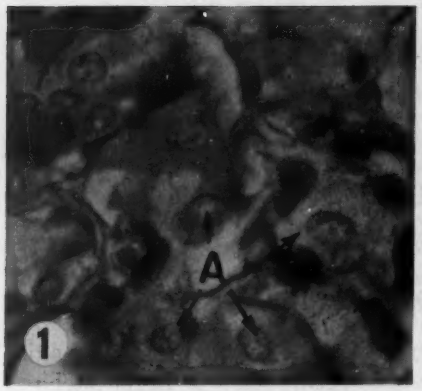
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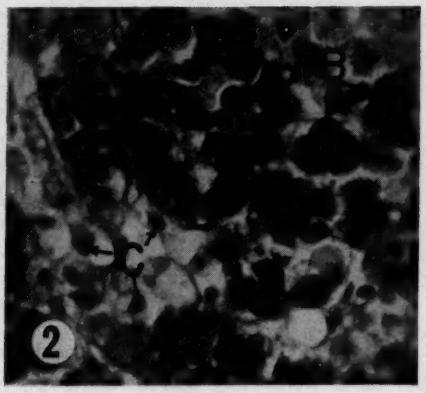
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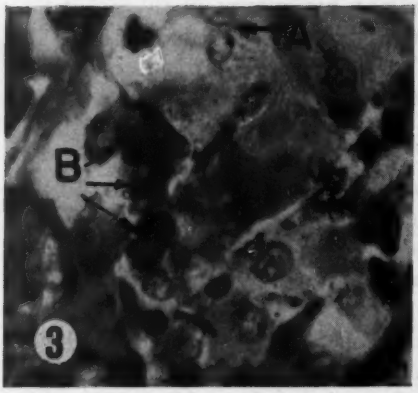
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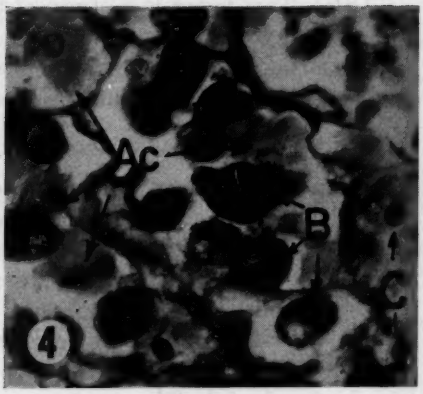
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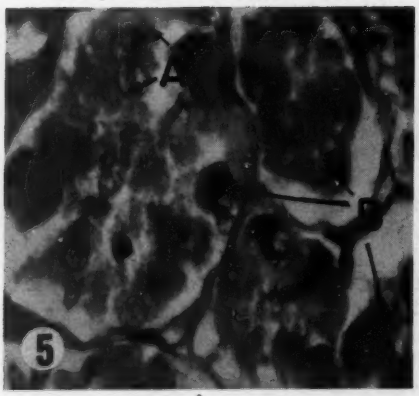
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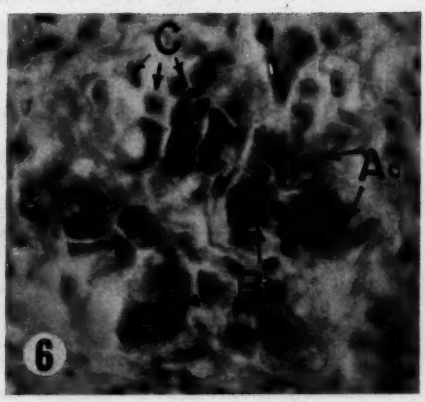
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intensely Schiff positive globules, particularly in very active glands (Figs. 1, 3 and 5). There is no standard terminology for these cells, which have been previously described as "thyreopriva cells" (5), "large chromophobes" (6), "transitional basophils" (7, 8), "modified acidophils" (9), or "intermediate mucoid cells" (10). As they can be stained red, blue, or lavender with the Mallory method, depending on minor variations in technique (4), they will be referred to here as "amphophils."

4. *Hypertrophic amphophils.* These cells are clearly derived from the amphophils by loss of cytoplasm and granules and enlargement of the nucleus. Occasionally the nucleolus may also enlarge to form a hyaline vesicle which nearly fills the nucleus. Morphologically, these cells correspond to the "thyroidectomy cells" of animals (4).

5. *Chromophobes:* These are cells with small nuclei and a small amount of cytoplasm in which no granules can be revealed by conventional staining methods (Fig. 4).

6. *Hyaline basophils.* These cells are derived from normal basophils through replacement of all or part of the granulated cytoplasm by opaque, hyaline, Schiff negative material. They are characteristically seen in spontaneous (11) or induced (12) hyperadrenocorticism.

Endocrine glands other than the hypophysis were studied with hematoxylin and eosin.

THYROID DEFICIENCY

Pertinent clinical and anatomic data on patients with thyroid deficiency are shown in Table 1. Autopsy material was available from 2 infants with

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FIG. 1. Hypophysis of Patient 1—untreated thyroid aplasia. **A.** Amphophils with large vesicular nuclei, sparse pale granules and indistinct cell boundaries. **B.** Normal basophil with dense, intensely Schiff positive granules. (PAS-Orange G, ×450)

FIG. 2. Hypophysis of Patient 2—treated thyroid aplasia. Note increased basophils (**B**), pycnotic nuclei in chromophobes (**C**), and scarcity of amphophils. (PAS-Orange G, ×450)

FIG. 3. Hypophysis of Patient 4—untreated myxedema secondary to thyroiditis. Note prevalence of amphophils (**A**), as in Patient 1. Basophils (**B**) are normal. (PAS-Orange G, ×450)

FIG. 4. Hypophysis of Patient 8—treated myxedema secondary to thyroiditis. Note normal basophils (**B**), acidophils (**Ac**) and chromophobes (**C**). No amphophils are seen in this field. (PAS-Orange G, ×450)

FIG. 5. Hypophysis of Patient 21—giant-cell carcinoma of the thyroid; no hormone treatment. Note large numbers of amphophils (**A**) and basophils (**B**). (PAS-Orange G, ×450)

FIG. 6. Hypophysis of Patient 27—giant-cell carcinoma of the thyroid treated with stilbestrol. Note basophils (**B**), acidophils (**Ac**), and pyknotic chromophobes (**C**). No amphophils are seen in this field. (PAS-Orange G, ×450)

TABLE 1. THE ENDOCRINE GLAN

Patient No.	Sex, Age	Diagnosis	Therapy	Hypophysis: Cells counted	Wt. (Gm.)	Amp.*	HA	Ac	NB	Chr	Hy
1 12,617	F 13 wks.	Thyroid aplasia. Aspiration of vomitus	None	5956	3-4x normal	35.8	1.9	5.5	5.6	51.2	—
2 16,616	M 18 mos.	Thyroid aplasia. Bronchopneumonia	Thyroid, gr.i q.d., 14 days	5390	0.18	5.2	0.5	5.0	14.8	74.5	—
Average, 6 normal infants (20)			None	*Mean* *S.D.*	*0.14* —	*3.8* *1.0*	*0.18* *0.08*	*16.7* *3.7*	*3.1* *1.2*	*76.3* *4.2*	
3 NEDH 156,272	F 32 yrs.	Thyroiditis. Hepatitis	None	4416	1.6	23.8	2.0	24.4	10.1	39.7	—
4 16,475	F 82 yrs.	Thyroiditis. Congestive heart failure	None	3587	0.99	27.7	2.1	20.0	13.6	36.6	—
5 10,695	F 36 yrs.	Total thyroidectomy, 5 mos. Carcinoma of the breast	None for 5 mos.	2127	"large"	17.1	2.9	20.5	26.2	33.3	—
6 WMH A54-78	F 43 yrs.	Thyroiditis. Diabetic coma. Hirsutism	Thyroid, 4 years. None for 30 days	4991	0.78	20.6	2.6	27.1	8.9	40.8	—
7 17,228	F 59 yrs.	Thyroiditis. Coronary sclerosis. Pulmonary emboli	Thyroid, 30-150 mg. q.d., 25 days. None for 12 days	2396	0.78	14.5	1.8	40.2	6.7	36.8	—
8 16,289	F 68 yrs.	Thyroiditis. Coronary thrombosis	Thyroid, 30 mg. q.d., for 11 yrs. to death	3973	0.42	12.2	1.6	31.9	5.6	48.5	0
Average, 11 normal postmenopausal women (14)			*None* *Mean* *S.D.*	*6063* —	*0.53* *0.10*	*5.5* *1.41*	*0.9* *0.34*	*33.4* *5.93*	*10.5* *3.50*	*49.7* *3.89*	—

* Amp. = amphophils.
Relative percentage:
HA = hypertrophic amphophils.
Ac = acidophils.
NB = normal basophils.
Chr = chromophobes.
HyB = hyaline basophils.

congenital thyroid aplasia. One of these patients (Case 1), previously reported in detail (13), was a 13-week-old female who had received no hormone therapy of any kind. The hypophysis was enlarged and there was a tenfold increase in amphophils and hypertrophic amphophils. Basophils were within normal limits, whereas acidophils were low (Fig. 1). The other infant with thyroid aplasia was an 18-month-old male who had been receiving 1 grain of thyroid per day for fourteen days before death. This hypophysis was much smaller and showed a striking decrease in amphophils and hypertrophic amphophils. The basophils had risen, a finding previously described in rats treated with thyroid hormone (1), but the acidophils remained low (Fig. 2).

THYROID DEFICIENCY

Thyroid	Adrenals	Gonads	Pancreas	Remarks
Total thyroid aplasia. Thyroglossal duct cyst.	6 Gm. Fetal cortex. Histochemistry as in adrenogenital syndrome	Follicle cysts. Stromal hyperplasia.	Hyperplastic islets. Severe fibrosis.	Case reported in full (13)
Thyroid aplasia. Thyroglossal duct cysts.	3.4 Gm. Normal	2.1 Gm. Normal immature tubules. Abundant Leydig cells	9 Gm. Normal	
9 Gm. Fibrosis. Lymphocytes (+). Hürthle cells	Moderate nodular hyperplasia	Follicle cysts. Active stroma. Thecomatosis	Normal	
11 Gm. Fibrosis. Lymphocytes (+++)	12 Gm. Moderate nodular hyperplasia	Ovarian fibromas (6 cm.), bilateral.	Normal	Arthritis, 5 yrs.
Surgically absent	Nodular hyperplasia	Pelvic radiation, 7 yrs. and 1 yr.	No data	
12 Gm. Fibrosis. Lymphocytes (+)	35 Gm. Linear cortex. Pyknotic nuclei	Cyst (6 cm.) Follicle cysts. Hyperplastic stroma	50 Gm. No sections available	Severe chronic cystic mastitis
9 Gm. Fibrosis. Lymphocytes (+++)	18.5 Gm. Slight nodular hyperplasia. Pyknotic nuclei	Severe stromal hyperplasia	70 Gm. Large, abundant islets	Mild cystic mastitis
6.5 Gm. Total fibrosis with foci of lymphocytes	18 Gm. Nodular hyperplasia	Surgically absent 20 yrs. (menorrhagia)	140 Gm. Normal	

Three adult women with untreated primary myxedema were also studied. In 2 (Cases 3 and 4) the thyroid had been virtually destroyed by unsuspected thyroiditis. In the third (Case 5) a total thyroidectomy had been performed in an unsuccessful attempt to arrest the growth of a carcinoma of the breast. In all 3 of these patients, as in the baby with untreated thyroid aplasia, the hypophysis was enlarged, amphophils and hypertrophic amphophils were increased, and acidophils were low (Fig. 3). Basophils were within normal limits in Cases 3 and 4. The increased basophils in Patient 5 may have been related to the carcinoma of the breast (14).

Three patients with myxedema secondary to thyroiditis had received varying amounts of thyroid hormone (Cases 6, 7, 8). With increasingly effective therapy there was a trend towards decreasing hypophyseal weight, decrease in amphophils and hypertrophic amphophils, and increase in acidophils (Fig. 4). Basophils were within normal limits in all 3 patients.

TABLE 2. THE ENDOCRINE GLAND

Patient No.	Sex, Age (yrs.)	Diagnosis	Therapy	Hypophysis: Cells counted	Wt. (Gm.)	Amp.*	HA	Ac	NB	Ch	Hbl
9 16,070	F 57	?Thyrotoxicosis. ?Acromegaly. Diabetes. Hirsutism. Calcific aortic stenosis. Exophthalmos	None	7666	0.90	14.0	1.6	25.9	6.8	51.7	—
10 16,299	F 55	Thyrotoxicosis. Cerebral hemorrhage	10.3 mc. I^{131}, 5 days	3442	0.35	21.6	2.4	33.8	20.4	21.8	—
11 15,028	F 39	Thyrotoxicosis. Exophthalmos. Rheumatic heart disease. Cerebral embolus	Propylthiouracil; KI; thyroidectomy, 4 years. 9 mc. I^{131}, 5 days	4520	0.47	11.6	1.1	30.3	7.1	49.9	—
12 15,570	F 63	(Thyrotoxicosis). Diabetes. Hirsutism. Duodenal ulcer. Mesenteric thrombosis	14 mc. I^{131}, 3 mos.	2827	0.45	7.2	3.3	21.4	14.0	52.9	1.2
13 16,242	F 57	(Thyrotoxicosis). Congestive heart failure. Pulmonary emboli	12 mc. I^{131}, 11 mos. 20 mc. I^{131}, 4 mos.	2263	0.29	18.5	2.3	29.8	12.6	36.1	0.7
14 16,731	F 67	(Thyrotoxicosis). Exophthalmos. Acromegaly. Diabetes. Hirsutism. Cerebrovascular accident	56.2 mc. I^{131}, 7 yrs.	5368	0.60	13.4	2.8	16.8	18.3	48.4	0.3
15 16,035	F 61	(Thyrotoxicosis). Gastric ulcer. Cerebrovascular accident	Propylthiouracil, 2 yrs.	6460	0.84	12.0	1.1	40.2	12.5	33.7	0.5
16 12,188	F 62	Thyrotoxicosis. Gastric ulcer. Congestive heart failure. Bronchopneumonia	Propylthiouracil, 0.6 Gm. q.d., and sat'd KI, 10 gtt. q.d., 5 days	3022	0.73	15.0	2.1	11.7	36.3	34.9	—
17 12,757	F 16	(Thyrotoxicosis). Exophthalmos. Postoperative cardiac arrest	Propylthiouracil, 0.6 Gm. q.d., 7 wks. Sat'd KI, 10 gtt. q.d., 12 days. Thyroidectomy terminal.	3842	—	10.6	1.4	24.8	9.6	53.6	—
18 8,057	M 59	(Thyrotoxicosis). Cerebral infarction. Bronchopneumonia	Sat'd KI, 10 gtt., q.d., 18 days. Thyroidectomy, 3 days	2525	—	1.1	2.0	46.0	2.3	48.6	—
Average, 11 normal postmenopausal women (14)			*None* *Mean* *S.D.*	*6063* —	*0.53* *0.10*	*5.5* *1.41*	*0.9* *0.34*	*33.4* *5.93*	*10.5* *3.50*	*49.7* *3.89*	—

* Relative percentage: Abbreviations as in footnote to Table 1.

The histology of the hypophysis in all of these patients with thyroid deficiency and the changes produced by thyroid medication suggest, although they do not prove, that the amphophil cells may be the source of thyrotropic hormone in man.

N THYROTOXICOSIS

Thyroid	Adrenals	Gonads	Pancreas	Remarks
46 Gm. Mild ocal hyperplasia	16 Gm. Linear cortex and thick reticularis	Severe stromal hyperplasia	60 Gm. Normal	Endometrial polyps. Secretion in breast
12 Gm. Coll d nodules	13 Gm. Narrow cortex	Severe stromal hyperplasia. Abundant hilar cells	90 Gm. Normal	Cystic hyperplasia of endometrium. Mild chronic cystic mastitis
12 Gm. No sections available	12 Gm. No sections available	Active stroma. Rare follicle cysts. Few ova	75 Gm. Normal	Onset of thyrotoxicosis during pregnancy
75 Gm. Multinodular goiter with focal involution	18 Gm. Adenoma (0.7 cm.) Large cortical nuclei	Surgically absent, 20 yrs. (pelvic inflammatory disease)	Focal fibrosis of islets	Hypertension. Central obesity
43 Gm. Multinodular goiter with fibrosis & involution.	20 Gm. Adenoma (1.5 cm.) Severe cortical hyperplasia	Severe stromal hyperplasia	140 Gm. Normal	Fibroid uterus. Endometrial polyps and hyperplasia
"Large" multinodular goiter with fibrosis & calcification	16 Gm. Severe nodular hyperplasia with atypical cells	Moderate stromal hyperplasia	75 Gm. Normal	Osteoma of skull. Lipoma. Arthritis
11 Gm. Small acini with vacuolated colloid	15 Gm. Mild nodular hyperplasia	No data	80 Gm. Normal	Bilateral simple mastectomies. Fibroid uterus
50 Gm. Nodular goiter	25 Gm. Nodular cortex with large, atypical nuclei	Surgically absent, 13 yrs. (fibroid uterus)	90 Gm. Very large, abundant islets.	Diabetic glucose-tolerance curve.
Subtotal resection	14 Gm. Normal cortex	Follicle cysts. Abundant, active stroma	80 Gm. Normal	Breast nodule
Subtotal resection	No data	No data	No data	

THYROTOXICOSIS

Data on patients with thyrotoxicosis are shown in Table 2. The histology of the hypophysis in untreated thyrotoxicosis had been well described prior to the introduction of the modern antithyroid drugs. The characteristic feature appeared to be an abundance of "transitional basophils" similar to those found in Addison's disease (7). Differential counts in a small

number of patients had failed to reveal any characteristic pattern of change in either normal basophils or acidophils (15).

In the material available for this report there was only 1 patient with clinical findings suggestive of thyrotoxicosis who had received no antithyroid medication. This woman (Case 9) was a 57-year-old hirsute diabetic whose coarse features and large extremities suggested mild acromegaly. Nervousness, excessive perspiration, mild exophthalmos, and serum protein-bound iodine levels of 9.8 and 7.7 gamma per 100 ml. were noted shortly before her death. The amphophils and hypertrophic amphophils were elevated, suggesting, but again not proving, increased production of TSH. Both basophils and acidophils were within normal limits.

Five patients had thyrotoxicosis treated with radioactive iodine. Two (Cases 10 and 11) died five days after they received the drug and were clinically toxic. Three patients (Cases 12, 13, 14) lived from three months to seven years after I^{131} treatment and were clinically euthyroid at the time of death. The only constant findings in any of these patients were moderately increased percentages of amphophils and hypertrophic amphophils. There was no consistent pattern of change in basophils, acidophils, or hypophyseal weight.

Intense hyperplasia of thyrotropic cells and actual hypophyseal adenomas have been induced in mice treated with radioactive iodine (2, 3, 4). However, the doses necessary to attain these effects were proportionately much larger than those employed in the treatment of human thyrotoxicosis. There is no evidence in the 5 patients presented here that the histology of the human hypophysis is significantly altered by therapeutic amounts of radioactive iodine, but observations on a larger number of patients dying longer periods after treatment will be necessary before a conclusion can be reached.

In 1 thyrotoxic patient treated with propylthiouracil alone for two years (Case 15), the hypophysis was somewhat enlarged and there was a moderate elevation in the numbers of amphophils and hypertrophic amphophils. In mice, like radioactive iodine, thiouracil derivatives will induce hyperplasia of thyrotropes and frank hypophyseal adenomas (16, 17). However, as in the case of I^{131}, the proportional dosages necessary for these effects are larger than those used therapeutically in man.

In 2 patients given propylthiouracil plus potassium iodide (Cases 16 and 17), there was no significant difference from the picture seen with propylthiouracil treatment alone. However, in 1 patient (Case 18) who had received only potassium iodide for eighteen days prior to death, there was a striking reduction in amphophils. This suggests that iodides may influence the human thyroid by inhibiting the production of thyrotropic hormone, as recently demonstrated in animals (18). Studies on a larger number of patients would be very desirable.

CANCER OF THE THYROID

Data on patients with cancer of the thyroid are summarized in Table 3. In 1 patient who received no treatment (Case 19), in 3 patients who died after terminal thyroidectomies (Cases 20, 21, 22), and in 1 patient treated with thyroidectomy and postoperative radiation (Case 23), the amphophils were consistently elevated. Hypertrophic amphophils were strikingly increased, a finding reported previously in women with carcinoma of the breast who had not received hormones (14). Basophils tended to be high, whereas acidophils varied greatly (Fig. 5). The findings in the hypophysis had no apparent relation to the histologic types of the thyroid tumors.

Four patients with cancers of the thyroid had received some type of antithyroid medication. One man (Case 24) had been taking thyroid hormone for three months but had received none for the last six weeks of life. The amphophils were elevated, just as they were in completely untreated patients. One woman (Case 25) had received large amounts of syrup of hydriodic acid. Amphophils were depressed, just as they were in Patient 18 who had been treated with potassium iodide. One patient (Case 26) had been given propylthiouracil and radioactive iodine, which might be expected to increase amphophils if they had any effect on the hypophysis. Terminally, he received a small amount of estrogen which, as previously shown (14), tends to depress the amphophils. At autopsy, however, amphophils were still at a high level. The final patient (Case 27) had been treated with estrogens alone. Amphophils were depressed to a normal level (Fig. 6). The antithyroid medication had no apparent effect on tumor growth in any of these patients.

Several of the patients are of particular interest, in that thyroid tumors developed in a setting suggestive of abnormal stimulation by the hypophysis. Thus Patient 20 had Reidel's thyroiditis and myxedema, conditions which, as shown earlier in this report, tend to increase the proportion of hypophyseal amphophils. Patients 22, 24 and 26 had goiters for many years before carcinomas developed. Patients 24 and 26 had mild and severe thyrotoxicosis, respectively.

These studies of human thyroid cancer do not prove that hypophyseal stimulation is involved in the pathogenesis of this disease. However, they do show that the amphophils, which seem to be the likeliest source of thyrotropic hormone, may be increased in these patients, and that these cells can be depressed by appropriate medication.

HYPOPHYSEAL TARGET ORGANS

Examination of the other endocrine glands showed a prevalence of hyperplastic phenomena in patients having a high percentage of amphophils in their hypophyses.

Adrenals. As reported previously (13), the baby with untreated thyroid

TABLE 3. THE ENDOCRINE GLAND[illegible] C

Patient		Diagnosis	Therapy	Hypophysis							
No.	Sex, Age (yrs.)			Cells counted	Wt. (Gm.)	Amp.*	HA	Ac	NB	Chr	Hyl
19 11,459	M 59	Undifferentiated Ca. of thyroid. Cerebral metastases	None	5626	0.84	14.8	4.4	29.4	20.8	30.6	—
20 13,659	F 78	Fibrosarcoma of thyroid. Riedel's thyroiditis. Bronchopneumonia	Tracheotomy+partial thyroidectomy, terminal	4141	0.50	16.1	3.4	37.8	11.1	31.6	—
21 14,946	M 61	Giant-cell Ca. of thyroid. Operative perforation of aorta	Subtotal thyroidectomy, terminal	5104	0.55	21.9	5.0	30.3	13.9	28.9	+
22 15,687	F 68	Undifferentiated Ca. of thyroid. Postoperative cardiac arrest	Radical thyroidectomy, terminal	6484	0.68	13.5	2.5	24.2	30.3	29.2	0.3
23 13,666	M 50	Ca. of thyroid, spindle-cell type. Bronchopneumonia	Subtotal thyroidectomy, 7 mos.; 6500 r postop. radiation	6617	0.56	10.5	2.8	21.9	15.7	49.1	—
24 11,798	M 57	Papillary adenocarc. of thyroid. †Thyrotoxicosis. Pulmonary metastases. Postradiation edema of glottis.	L. hemithyroidectomy, 1 yr.; 5500 r postop. radiation; thyroid, 0.2 Gm. q.d., 3 mos.; no hormone, 6 wks.	5441	0.64	18.7	2.2	48.0	15.5	15.6	—
25 15,588	F 67	Squamous & papillary Ca. of thyroid. Pyelonephritis. Bronchopneumonia	L. hemithyroidectomy, 5 mos.; 5000 r postop. radiation; syrup HI, 24 cc. q.d., 21 days; none for 4 mos.	8174	0.82	6.2	2.9	40.5	9.4	40.9	0.1
26 14,394	M 54	Adenocarcinoma of thyroid. Thyrotoxicosis. Pulmonary metastases	Propylthiouracil, 1 mo.; 102 mc. I^{131}, 3 wks.; Ovocyclin, 1.66 mg. q.d., 5 days	2179	—	19.9	5.2	31.6	3.5	39.8	—
27 12,471	M 51	Giant-cell Ca. of thyroid. Pulmonary metastases. Aspiration pneumonia	Subtotal thyroidectomy, 5 mos.; 3700 r postop. radiation; stilbestrol, 15 mg. q.d., 12 days; none for 12 days	2776	—	5.2	3.6	43.5	6.4	41.3	—
Average 11 normal postmenopausal women (14)			*None* *Mean* *S.D.*	*6063* —	*0.53* *0.10*	*5.5* *1.41*	*0.9* *0.34*	*33.4* *5.93*	*10.5* *3.50*	*49.7* *3.89*	— —

* Relative percentage. Abbreviations as in Footnote to Table 1.

aplasia (Case 1), had a persistent fetal cortex and histochemical findings in the adrenals similar to those in infants with the adrenogenital syndrome. The adrenals of the infant who had been treated for thyroid aplasia (Case 2) were essentially normal. The 6 myxedematous adults tended to have unusually large adrenals, or a nodular growth pattern of the cortex, or both. One woman (Case 6) was hirsute. Treatment with thyroid hormone tended to decrease the size of cortical nuclei and to increase the size of stored lipoid droplets.

Five of the 10 patients with thyrotoxicosis had anatomically hyper-

N CANCER OF THE THYROID

Thyroid	Adrenals	Gonads	Pancreas	Remarks
Tumor replacing left lobe of thyroid. Right lobe not involved	20 Gm. Moderate cortical hyperplasia	No data	No data	
Both lobes replaced by tumor, lymphocytes and fibrosis	18 Gm. Severe nodular hyperplasia	Surgically absent, 8 yrs. (adenoacanthoma of endometrium)	80 Gm.	Hyperostosis frontalis interna
Left lobe resected. Right lobe not involved	22 Gm. No sections available.	No data	115 Gm.	
No thyroid or tumor tissue remaining in neck	18 Gm. Linear cortex. Large nuclei	Moderate amount of inactive stroma	90 Gm. Numerous hyperplastic islets	Multinodular goiter for 30 yrs.
Right lobe replaced by tumor. Left lobe subtotally resected.	23 Gm. Very large, atypical cortical cells	Hypospermatogenesis with focal atrophy	50 Gm. Numerous large islets	
Left lobe replaced by tumor. Right showed focal hyperplasia & involution	30 Gm. Nodular hyperplasia	Hypospermatogenesis. Tubular thickening. Normal Leydig cells	Uuusually large & abundant islets	Goiter for 8 yrs.
Left lobe resected. Right partially infiltrated by tumor	17 Gm. Nodular hyperplasia. Very large nuclei	Serous cyst of ovary (2.5 cm.)	60 Gm.	Basal cell Ca. of cheek
125 Gm. Right lobe replaced by tumor. Left lobe & isthmus hyperplastic	34 Gm. Nodular hyperplasia	Severe tubular fibrosis. Decreased Leydig cells	90 Gm. Large, abundant islets with giant nuclei	Goiter for 12 yrs. Active duodenal ulcer. Arthritis of spine
Right lobe replaced by tumor. Left lobe not involved	15 Gm. Thick nodular cortex	No data	Abundant islets; some very large	Hemangioma of liver

plastic adrenals. Two patients (Nos. 12 and 13) had frank adrenal adenomas. One of these (Case 12) had hypertension, diabetes, and central obesity of the Cushing type. Three women were hirsute (Nos. 9, 12 and 14). Although an increased 17-ketosteroid excretion was not demonstrated in any of these patients, it is of interest that in 4 cases (Nos. 12, 13, 14 and 15) the hypophysis had appreciable numbers of hyaline basophils. Adrenal hyperplasia was present in all 9 of the patients with thyroid cancer.

Gonads. The ovaries of the patients with a high count of amphophils

tended to show stromal hyperplasia. This was most striking in Patient 4, an 82-year-old woman with untreated thyroiditis, who had bilateral ovarian fibromas measuring 6 cm. in diameter. The occurrence of a small ovarian fibroma has been reported previously in an elderly woman who had a high count of amphophils secondary to inadequately treated Addison's disease (19). Three women (Cases 8, 12 and 16) were surgical castrates. Patient 5 had a premature menopause induced by radiation, again in an attempt to arrest the growth of breast carcinoma.

The testes of Patient 2, the 18-month-old cretin who had received thyroid, were normal for his age. The 3 adult men (aged 50 to 57) with cancer of the thyroid whose testes could be studied showed varying degrees of hypospermatogenesis and testicular atrophy.

Pancreas. As previously reported in patients with adrenal insufficiency (19), some but not all of the patients with high counts of amphophils had unusually large or abundant islands of Langerhans. These were seen in 2 patients with thyroid deficiency (Cases 1 and 7), 1 patient with thyrotoxicosis (No. 16), and 5 patients with cancer of the thyroid (Cases 22, 23, 24, 26 and 27). One patient with myxedema had diabetes mellitus (Case 6). Three patients with thyrotoxicosis had clinical diabetes mellitus (Cases 9, 12 and 14) and one had a diabetic glucose-tolerance curve (Case 16).

Bones and joints. One woman with thyrotoxicosis had frank acromegaly (Case 14). Another had physical findings highly suggestive of this disease, but radiologists were unwilling to make the diagnosis from the skeletal changes alone (Case 9). It is of interest that neither of these women had a hypophyseal adenoma, true acidophils were slightly to significantly decreased, and in both patients the amphophils and hypertrophic amphophils were increased. One woman with cancer of the thyroid had hyperostosis frontalis interna (Case 20). This condition has been previously linked with increased hypertrophic amphophils and "sparsely granulated basophils" in the hypophysis (20). It is thought by some to be a variant of acromegaly (21). Arthritis was noted in Patients 4, 14 and 26. This disease has been produced in mice by radiothyroidectomy (22).

Secondary sex organs. Seven women with increased percentages of amphophils had hyperplastic endometrial or mammary glands (Cases 6, 7, 9, 10, 13, 15 and 17). This finding has also been reported in mice in which amphophil adenomas had been induced by I^{131} (23).

DISCUSSION

Study of the human hypophysis in a variety of endocrine disorders not directly related to the thyroid has suggested that the amphophils may produce a number of tropic hormones besides TSH. Thus, in inadequately treated primary Addison's disease, the amphophils may increase to as

much as 50 per cent of the total differential count, suggesting that they produce adrenocorticotropic as well as thyrotropic hormone (19). The similarity of the human hypophysis in Addison's disease and thyrotoxicosis has been previously noted by Kraus (7); and Crooke and Russell (24) have commented on the similar pathologic findings in the thyroid in the two conditions. Although many patients with Addison's disease have low indices of thyroid function secondary to thyroiditis (25), the simultaneous occurrence of Addison's disease and thyrotoxicosis has been reported (26, 27). The hyperplastic adrenals noted in many of the patients of this report might also indicate associated production of ACTH and TSH.

A common origin of ACTH and TSH from the same family of cells in the hypophysis might explain the frequently observed exacerbations of thyrotoxicosis with the relative adrenal insufficiency of stress. Cortisone, which suppresses the amphophils (19), has been reported to be of clinical benefit in several conditions which might conceivably be associated with increased TSH production (28–30).

The association of amphophil hyperplasia with Klinefelter's syndrome (31), ovarian stromal hyperplasia (32), and high titers of stored gonadotropins in the hypophysis (33) suggests that amphophils may produce some type of gonadotropin as well as TSH and ACTH. The prevalence of ovarian stromal hyperplasia in the women with thyroid disease reported here, and the occurrence of large ovarian fibromas in Patient 4 are of great interest in this respect. In 2 women thyrotoxicosis developed following surgical castration (Cases 12 and 16), and in another a thyroid tumor developed (Case 20). The origin of gonadotropins and TSH from the same family of hypophyseal cells may explain the clinical association of thyroid and pelvic disease in women (34) and the onset of thyrotoxicosis in elderly individuals of either sex with profound gonadal atrophy.

Although their function in pregnancy is not certainly known, the amphophils appear to be the "pregnancy cells" which have been described in the human hypophysis (32). It has recently been reported that the concentration of serum protein-bound iodine rises to near thyrotoxic levels in normal pregnancy (35). The onset or exacerbation of clinical thyrotoxicosis with pregnancy is also seen and, indeed, occurred in Patient 11 of this report.

The association of acromegaly and thyrotoxicosis, as noted in Patient 14 and possibly in Patient 9, is also not unusual and could be explained by a common origin of TSH and growth hormone. In mice there has been experimental production of hypophyseal tumors which clearly secrete both TSH and growth hormone (36).

The work reported here is necessarily based on very small numbers of cases and is far from conclusive. However, it does suggest that a common

origin of TSH, ACTH, gonadotropin, and growth hormone from the hypophyseal amphophils may explain a number of clinically important interrelationships of the thyroid with the adrenals, gonads, pregnancy, and growth disorders.

SUMMARY

Differential cell counts were performed on the hypophyses of 8 patients with primary thyroid deficiency, 10 patients with a history of thyrotoxicosis, and 9 patients with cancer of the thyroid. All glands were stained with the periodic-acid Schiff Orange G technique which differentiates three types of chromophils—densely granulated, Schiff positive basophils; densely granulated, Schiff negative acidophils; and sparsely granulated, weakly Schiff positive amphophils.

In the cases of untreated thyroid deficiency, the hypophysis was enlarged. There was intense hyperplasia of amphophils, and a decrease in acidophils, whereas basophils were often within normal limits. Treatment with thyroid hormone decreased both the hypophyseal weight and the relative percentage of amphophils, while increasing the acidophils. This suggests that the amphophils may be the source of thyrotropic hormone in man.

Untreated thyrotoxicosis appeared to be characterized by a moderate increase in the amphophils, suggesting increased production of thyrotropic hormone. Amphophils were also moderately increased in the hypophyses of 5 patients treated with radioactive iodine, in 1 patient treated with propylthiouracil, and in 2 patients treated with propylthiouracil plus potassium iodide. There was a profound reduction in amphophils in 1 patient treated with potassium iodide alone.

Amphophils were increased in patients with thyroid cancer, again suggesting an increased production of thyrotropic hormone. Amphophils were decreased following administration of syrup of hydriodic acid in 1 patient, and following administration of estrogen in another. However, there was no clinical regression of the thyroid tumor in either instance.

Evidence has been presented which suggests that the amphophils may secrete not only TSH but ACTH, a gonadotropin, and growth hormone. This concept has been applied in a discussion of possible etiologic mechanisms of thyrotoxicosis.

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THE AMOUNT OF TISSUE TO BE PRESERVED AT SUBTOTAL THYROIDECTOMY: AN ESTIMATE BASED ON SERIAL ISOTOPE TRACER MEASUREMENTS*

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IDEALLY, the optimum amount of thyroid parenchyma to be preserved at thyroidectomy for an overfunctioning thyroid gland is that amount which will assure a euthyroid postoperative state and at the same time reduce to a minimum the danger of recurrent hyperthyroidism. Generally speaking, this is the smallest quantity of tissue compatible with euthyroidism, since, other factors being equal, the smaller the tissue remnant the less the probability of recurrence.

There are serious and obvious difficulties in the way of determining the exact dimensions of such an optimal parenchymal remnant in the traditional clinical manner. In a purely clinical method of estimation, the size of the remnant would be judged on the basis of the visual impression of the surgeon, and this intelligent guess would then be correlated with the clinical course of the disease. Visual impressions are deceptive, and their correlation with clinical manifestations, the assessment of which is likewise often a matter of subjective judgment, will not yield precise data. It is not surprising, therefore, that the amount of thyroid tissue spared at thyroidectomy has ranged widely among surgeons. A survey of the relevant recommendations in several popular textbooks (1–6) and in competent technical writings (7, 8) has shown irreconcilable divergences in advice. The following list, containing the names of the authors and their recommendations, is a representative one: Pemberton (1, 2), 15 to 35 per cent of each lobe (or, on the basis of an average weight of 30 Gm. for the thyroid gland, 4.5 to 10.5 Gm. of tissue); Rienhoff (5), one-tenth of the gland (or, on the basis just mentioned, 3.0 Gm.); Cattell (7), 2.0 Gm. of

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tissue on each side; and Joll (quoted by Troell (8)), one-tenth to one-fourth of the gland (3.0 to 7.5 Gm.). Baxter (4) summarized the variability of these opinions succinctly when he stated that the amount of tissue to be left is a matter of personal preference. It is, moreover, to be expected that, in the absence of any quantitative guide, the general tendency in deciding the size of the parenchymal remnant has been toward the conservative policy of leaving too much rather than too little. It has generally been thought that through such conservatism one may not only lighten the technical difficulties but presumably also guard against the danger of hypothyroidism, which often is regarded as a prompt and annoying sequela of too-radical surgery. A notable exception to this trend has been Bartlett's advocacy (9) of thyroidectomy of such radicality as to produce hypothyroidism.

We have approached this problem with an attitude conditioned by our earlier experiences with the growth potentiality of thyroid parenchyma. Studies of cases of so-called total thyroidectomy had shown that even grossly indistinguishable bits of thyroid tissue left in situ are capable of growth and of eventual clinically demonstrable function (10). Later observations revealed that very small thyroid autotransplants have the same capacity (11). It seemed logical to assume, therefore, that remnants of thyroid parenchyma preserved at thyroidectomy would be characterized by a similar vigor of survival and growth potentiality. If this assumption were correct, then it would be possible to arrive at the optimum size of the thyroid remnant by observing the postoperative fate of tissue rests (of varying, but always very small size) left in place at operation. Using radioiodine tracer technics in addition to conventional clinical methods of study, we carried out such an investigation in 25 patients. A survey failed to show bibliographic reference to clinical investigation of this kind, but in animals Johansen *et al.* performed similar experiments employing tracer technics (12).

CLINICAL MATERIAL AND METHODS

The 25 patients studied fall into 3 groups: Group I, diffuse thyroid hyperplasia (Graves' disease), 10 cases; Group II, toxic nodular goiter, 9 cases; and Group III, nontoxic nodular goiter, 6 cases (Table 1). Nontoxic nodular goiters were included mainly for the purpose of comparison; in their surgical management the size of the remnant is not of great concern, and is usually dependent on the type and extent of pathologic changes. The pertinent preoperative clinical data on these patients are summarized in Table 1.

The operations were planned so as to remove *more* tissue than would be thought desirable by conventional standards. The parenchymal remnants

were, however, graded in the sense that larger amounts were left in place in cases that showed less clinical thyroid activity. Within each category, variations in the size of the remnant were allowed in order to approach, by trial and error, the unknown ideal amount. It was not thought to be either desirable or necessary to explore the opposite approach to determination of the optimal size of the remnant (from the direction of excessive amounts of tissue through decreasing amounts) and leave amounts of tissue such as

TABLE 1. PREOPERATIVE AND POSTOPERATIVE THYROID FUNCTION*

Group	Serial No.	BMR (%)		Blood cholesterol (mg./100 ml.)		Blood PBI (μg./100 ml.)		I^{131} excretion (% per 96 hrs.)		Length of observation (mos.)	Postop. state
		Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.		
I	1	+45	− 3	133	152	—	4.2	—	56	32	Euthyroid
	2	+43	−17	136	296	—	2.2	13	—	21	Mildly hypothyroid
	3	+71	−29	112	169	18.4	0.6	—	82	17	Hypothyroid
	4	+61	−20	—	358	—	1.5	—	—	17	Hypothyroid
	5	+109	−19	90	—	—	—	—	80	26	Euthyroid
	6	+57	−20	—	158	—	3.5	19.5	83	18	Euthyroid
	7	+79	−15	76	218	15.4	2.5	—	—	12	Euthyroid
	8	+78	− 8	77	142	22.4	3.5	10.0	—	12	Euthyroid
	9	+74	+ 2	55	320	21.7	—	—	—	13	Euthyroid
	10	+52	−13	139	160	—	5.7	—	72	10	Euthyroid
II	11	+30	−12	168	246	3.5	2.6	—	—	21	Euthyroid
	12	+16	+14	218	188	3.7	5.6	52.0	—	23	Euthyroid
	13	+32	−23	138	308	10.8	1.4	—	—	18	Hypothyroid
	14	+26	−22	141	268	14.1	0.6	75	—	19	Mildly hypothyroid
	15	+98	−22	130	246	—	1.7	—	99	14	Hypothyroid
	16	+85	−33	139	354	—	0.5	—	—	18	Hypothyroid
	17	+35	−12	—	166	—	4.6	—	73	24	Euthyroid
	18	+72	−18	50	193	29.4	6.7	12	—	13	Euthyroid
	19	+50	+ 3	—	202	—	—	—	64	12	Euthyroid
III	20	+13	−26	—	200	—	2.5	—	74	18	Hypothyroid
	21	− 6	−15	192	229	—	3.3	—	75	17	Euthyroid
	22	− 6	−34	—	267	8.2	1.6	47	85	11	Hypothyroid
	23	−10	−13	149	354	—	5.5	—	—	18	Euthyroid
	24	+ 1	−13	126	137	—	6.2	—	—	18	Euthyroid
	25	− 2	−20	143	250	—	1.0	—	84	14	Mildly hypothyroid

* These values represent the results of the last determination before and after operation.

would be likely to cause persistent or recurrent hyperthyroidism. Not only did the chosen method seem ample and valid in itself but it was felt that subjecting the patients deliberately to the annoyances and dangers of persistent or recurrent hyperthyroidism was not justified.

In order to control the size of the remnants, an "anatomic" thyroidectomy was used, with visualization of the recurrent laryngeal nerves and parathyroid bodies. The size of the remnant was estimated by matching it as accurately as possible with a piece of tissue cut from a similar portion of the resected gland, and weighing the latter. It was found by control

measurements that this method of "matched weights" is accurate within a margin of error of ±10 per cent. In 8 cases, in addition to the remnant left in the usual anatomic location, an autotransplant was made to the sternocleidomastoid muscle of the opposite side; in 1 case, only a transplant was left. Other studies (11) have shown that autotransplants of this type behave like remnants, and therefore their inclusion in the series is justified.

The patients were prepared for operation in the routine manner, except when preoperative I^{131} tracer studies were made. Postoperatively the usual

TABLE 2. I^{131} UPTAKE AFTER THYROIDECTOMY

Group	Serial No.	Preoperative uptake (counts/sec.)	Size of thyroid remnant (mg.)	Postoperative uptake (counts/sec.)			
				I*	II	III	IV
I	1	—	4000	—	—	20.0	22.0
	2	—	40	—	0.8	1.0	—
	3	—	60	2.5	1.1	1.0	1.8
	4	37	150	1.6	1.8	15.0	—
	5	57	650	—	2.7	9.0	—
	6	50	360	1.0	1.0	6.0	—
	7	43	350	19.0	27.0	—	—
	8	79	830	6.0	3.7	30.0	29.0
	9	49	1250	1.2	3.7	11.5	11.0
	10	—	1650	2.6	21.0	65.0	48.0
II	11	—	1500	2.0	—	7.8	22.0
	12	20	5000	25.0	20.0	49.0	—
	13	—	75	—	3.0	8.5	—
	14	—	275	—	12.0	3.0	13.0
	15	—	80	—	2.7	2.7	2.6
	16	—	400	11.0	1.5	6.0	6.0
	17**	—	0	—	2.4	31.0	—
	18	53	720	1.6	1.8	10.0	4.0
	19	—	1200	2.3	26.0	51.0	46.0
III	20	—	75	—	—	3.5	3.0
	21	—	2000	11.0	12.0	33.0	—
	22**	—	3000	3.7	2.0	1.5	—
	23	—	1200	1.9	2.8	0.3	1.5
	24	—	5000	4.6	5.2	17.0	37.0
	25	—	890	2.2	3.1	3.5	16.0

* The numerals I to IV denote periods of postoperative study; the intervals between the times of study varied from three to six months.

** *See* text.

management was likewise followed, except that, regardless of the appearance of hypothyroid symptoms, no thyroid substitution therapy was administered until at least two postoperative I^{131} tracer determinations had been carried out. At intervals of three to six months for periods of from ten to twenty-six months the function of the remaining thyroid parenchyma was investigated by clinical examination, by determination of the basal metabolic rate (Benedict-Roth technic), blood protein-bound iodine level (method of Barker (13)) and blood cholesterol level, and by I^{131} uptake and excretion studies.

For the tracer studies the patients were hospitalized for seventy-two to ninety-six hours. The oral radioiodine (I^{131}) tracer dose was 50 microcuries and the methodology of determining thyroidal uptake and urinary excretion was the same as described by us in previous reports (19). With the technic of contact scanning employed, counts of 1 or more per second over any area scanned denotes the presence of some active thyroid tissue; a normal thyroid gland gives a reading of 6–12 counts in each field over the two lateral and central scanning areas. Earlier investigations (10), confirmed by the experience here recorded, revealed that in dealing with very small remnants a total count of 6 per second is the lower limit of uptake associated with clinical euthyroidism; the usual normal range in these instances is 10–25 counts per second. Whereas contact scanning is well suited to the study of small tissue rests such as those involved in this investigation, it is not a quantitative measure, in itself, of total thyroid function. For the latter, reliance was placed whenever possible on results of the excretion studies and their correlation with other thyroid functional indices. The normal urinary 96-hour I^{131} excretion with the method used is from 75 to 50 per cent.

RESULTS AND DISCUSSION

The results of the clinical and tracer studies are presented in Tables 2 and 3 and Figures 1, 2 and 3.

Certain restrictions inherent in the method of study, case selection, and uncontrollable biologic variables persistently associated with clinical experiments must be kept in mind when one attempts to interpret the findings. The scanning technic, no matter how carefully performed, has unavoidable sources of error that may be the cause of some inconsistency in the results. More important, the three groups of patients were not truly homogeneous even within the assigned category, and the number of patients in each group was not large enough to smooth out the unevenness of the material. A further factor of variability was introduced by the wide range of planned differences in the size of the tissue remnants—no two being exactly alike. Thus it was to be expected that the findings would not

TABLE 3. MEAN UPTAKE BY GROUP

Group	Counts per second			
	I*	II	III	IV
I	4.8	6.9	17.6	22.5
II	8.3	8.7	18.7	15.7
III	4.1	5.2	12.8	14.3

* The numerals I to IV denote periods of postoperative study; the intervals between the times of study varied from three to six months.

be entirely consistent. Nevertheless, certain definite trends could be discerned with a good degree of certainty.

The interpretation of these trends must concern itself with two distinct problems; first, with the survival and rate of growth of the remnants as reflected in the changes of their functional state (*i.e.*, avidity for iodine) and secondly, with the relationship of these changes to the clinical state of the patient. In the latter relationship may lie the answer to the main

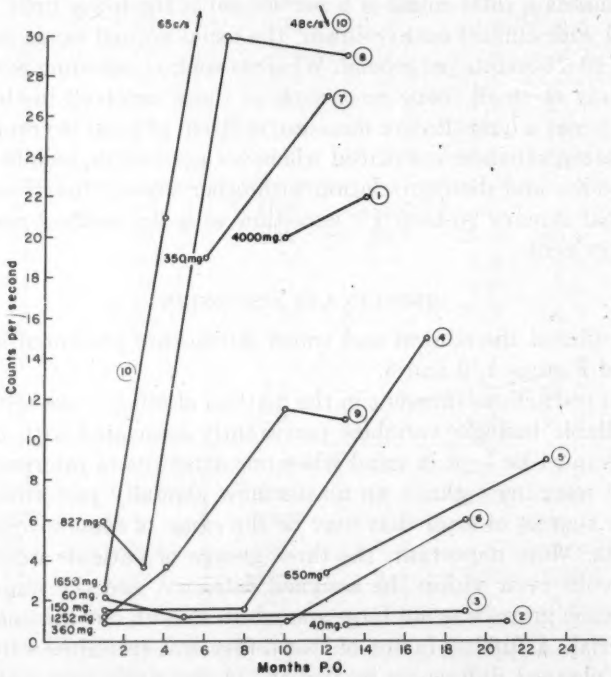

FIG. 1. Postoperative thyroidal I^{131} uptake in Group I (diffuse toxic goiter).

question of this inquiry, namely, the optimum size of the parenchymal remnant.

As regards the functional changes, among the 25 parenchymal remnants 18 showed a very definite and generally progressive increase in the capacity for iodine uptake. Among the 7 cases that failed to show a significant increase in functional activity, in 4 the remnants were of exceedingly small—and, in retrospect, grossly inadequate—size (40 to 80 mg., Cases 2, 3, 15

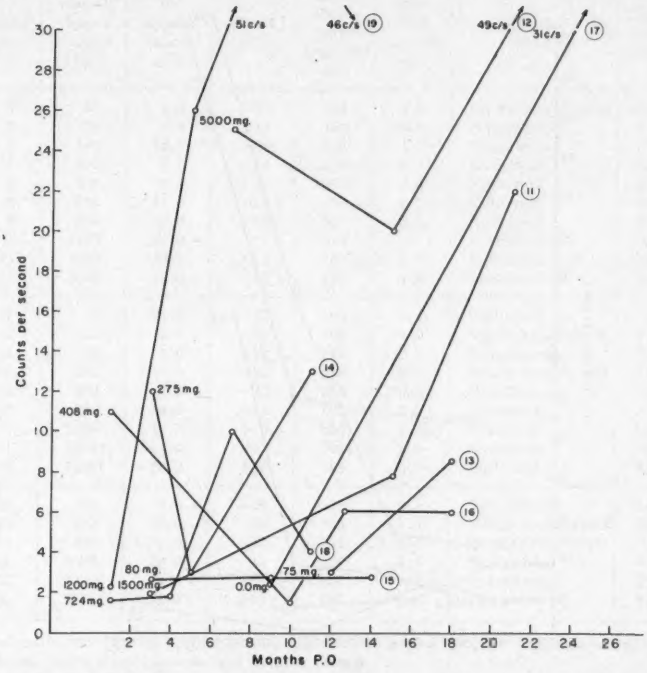

FIG. 2. Postoperative thyroidal I^{131} uptake in Group II (toxic nodular goiter).

and 20). This fact made investigation difficult and less accurate. In another case of this group the initial drop in activity was followed by a rise to a low-normal level without, however, reaching the original plateau (Case 16). In the remaining 2 cases, both nontoxic nodular goiter, the remnants were of a histologic type with little or no regenerative propensity (Cases 22 and 23); this was particularly true in Case 22, which was the only remnant which showed a persistent and progressive decline of activity (*see* subsequent comments).

Comparing the cases according to group classification on the basis of the mean values of uptake (Table 3), the increase in functional capacity was

greater in the hyperthyroid groups, and among these it was greater in the group of diffuse hyperplasia. These differences, however, were not marked. It should again be remembered that by experimental design the average weight of the remnant was, in general, inversely proportional to the degree of preoperative thyroid activity—a fact that tended to even up the differences in the intrinsic growth potentiality among the various groups.

From the findings it appears that, under the conditions of these observa-

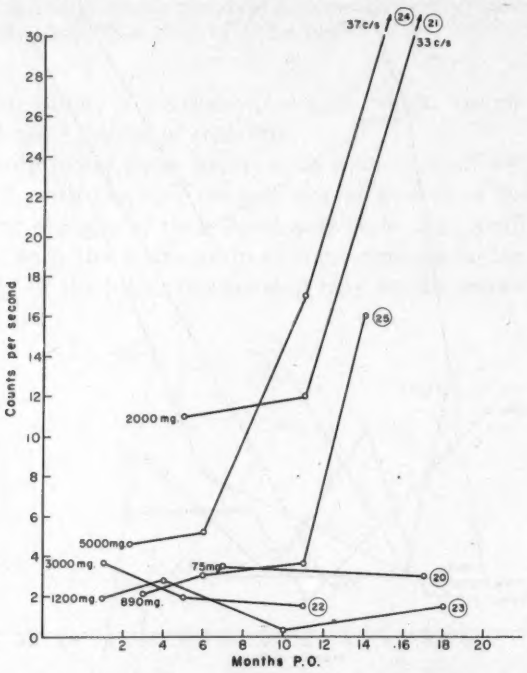

FIG. 3. Postoperative thyroidal I^{131} uptake in Group III (nontoxic nodular goiter).

tions, fragments of thyroid parenchyma left *in situ* (or transplanted with a predetermined technic) will survive and, in most instances, grow. Johansen and his co-workers reached similar conclusions in animal experiments (12).

The next phase of this inquiry concerns the conditions under which the degree of growth of these remnants is sufficient to assure euthyroidism.

The data pertinent to this question are summarized in Table 4. In this table are listed the sizes of the remnants by group, in ascending order of magnitude, and against each is the respective information concerning the

postoperative state of thyroid function. With a few conspicuous exceptions, there is a fairly orderly relationship between the size of the remnant and the postoperative state, conditioned to a discernible degree by the pathologic type of the original lesion. The cases that sharply deviate from this trend had unusual clinical features. In Case 17 of Group II (total

TABLE 4. SIZE OF THYROID REMNANT AND POSTOPERATIVE THYROID FUNCTION*

Group	Serial No.	Size of thyroid remnant (mg.)	I^{131} uptake (counts/sec.)	BMR (%)	Blood cholesterol (mg./100 ml.)	Blood PBI (μg./100 ml.)	Clinical state	Thyroid medication	Length of follow-up (mos.)
I	2	40	1.0	−17	296	2.2	Mildly hypothyroid	Yes	21
	3	60	1.8	−18	169	0.6	Hypothyroid	Yes	17
	4	150	15.0	−20	358	1.5	Hypothyroid	No	17
	7	350	9.0	−15	218	2.5	Euthyroid	No	12
	6	360	6.0	−20	158	3.5	Euthyroid	No	18
	5	650	27.0	−19	120	2.7	Euthyroid	No	26
	8	830	29.0	−19	233	3.5	Euthyroid	No	12
	9	1250	22.0	+ 2	320	—	Euthyroid	No	13
	10	1650	48.0	−13	160	5.7	Euthyroid	No	10
	11	4000	22.0	− 3	152	4.2	Euthyroid	No	32
II	17**	0?	31.0	−12	166	4.6	Euthyroid	No	24
	13	75	8.5	−23	308	1.4	Mildly hypothyroid	Yes	18
	15	80	2.6	−22	246	1.7	Hypothyroid	Yes	14
	14	275	13.0	−22	268	0.6	Mildly hypothyroid	Yes	19
	16	400	6.0	−33	268	0.5	Hypothyroid	Yes	18
	18	720	4.0	−18	192	6.7	Euthyroid	No	13
	19	1200	46.0	+ 3	202	4.9	Euthyroid	No	12
	11	1500†	22.0	−12	246	2.6	Euthyroid	No	21
	12	5000†	25.0	+14	188	5.0	Euthyroid	No	23
III	20	75	3.0	−26	200	2.5	Hypothyroid	Yes	18
	25	890	16.0	−20	250	1.0	Mildly hypothyroid	Yes	14
	23	1200	1.5	−13	354	5.5	Mildly hypothyroid	No	18
	21	2000	33.0	−15	229	3.3	Euthyroid	No	17
	22	3000‡	1.5	−34	267	1.6	Hypothyroid	Yes	11
	24	5000†	27.0	−13	137	6.2	Euthyroid	No	18

* The values for postoperative thyroid function represent the results of the last determination after operation.
** No grossly visible thyroid remnant (*see* text).
† Estimate of size of lobe.
‡ *See* text.

thyroidectomy), originally it had been assumed that all the thyroid parenchyma had been removed. Five years postoperatively distinct evidences of thyroid function were noted and during the period of observation recorded in Table 2 these signs increased rapidly. All the detectable uptake activity was centered in the thyroid area, thus eliminating the obvious assumption that there was ectopic thyroid tissue present. Undoubtedly, by oversight, a small but significant fragment of parenchyma had been left behind. In Case 22 of Group III, there was a distinctly adequate remnant (3,000 mg.) but low thyroid function. Although the clinical diagnosis was typical nodular goiter, on microscopic examination of the removed thyroid

gland early Hashimoto's struma was found. The poorly functioning thyroid tissue was further compromised by the postoperative progress of this disease.

Whereas it is fairly evident that with an increase of the size of the remnant there is a roughly parallel rise in the level of postoperative thyroid function, it is less apparent at what level on the scale of sizes one may place the point denoting the correspondence between the smallest remnant size and the lower limit of the euthyroid state—that is, the point denoting the optimal quantity of parenchyma to be preserved. Because of the wide scatter of the so-called normal values of the indices of thyroid function, such as BMR, blood cholesterol and blood PBI levels, a sharp line of demarcation cannot be expected. Taking into a synoptic account all the laboratory indices including the results of I^{131} tracer uptake studies and, in particular, the clinical state of the patients, a dividing band can be drawn between the amounts of tissue that are inadequate and those that are adequate to insure euthyroidism. In Group I this band ran through the cases having remnants weighing 650 and 820 mg.[1] (Cases 5 and 8). Among patients with smaller remnants, 3 were manifestly hypothyroid (Cases 2, 3 and 4) and in 2, although they were clinically euthyroid, the uptake results were in or near the hypothyroid range. The smallest amount of tissue, therefore, that in this group assured a satisfactory clinical state of thyroid function appeared to be between 600 and 800 mg. In Group II the band of division between insufficient and sufficient amounts of tissue passed through Cases 18 and 19, in which the remnants weighed 720 and 1,200 mg. respectively. Since, unfortunately, there was no case studied in the range between these two widely separated values one can only surmise that the figure of 1,000 mg. would correspond very closely to the optimum amount. In Group III the line of demarcation is less secure but also less important; in this category of patients the factor determining the amount of tissue to be spared is not the likelihood of recurrent hyperthyroidism but the pathologic characteristics of the lesion, which vary greatly from case to case. Excluding Case 22, the uncommon features of which have already been noted, among these cases satisfactory thyroid function was noted with 2,000-mg. and 5,000-mg. amounts of tissue. It may probably be concluded, therefore, that in nontoxic nodular goiters the preservation of from 3 to 5 grams of *normal* thyroid parenchyma will insure satisfactory postoperative thyroid function.

A word of explanation is in order with respect to the low thyroid func-

[1] For the visualization of the dimensions of these pieces of tissue one should remember that a bit of thyroid parenchyma $1 \times 1 \times 0.5$ cm. in size weighs about 500 mg.; this is about twice the size of the rubber tip of an ordinary writing pencil.

tional indices in most of the cases in this series. The operative procedures were purposely designed to maintain thyroid function at or below the low normal level. A further comment is needed, however, on the low values obtained in the functional tests in cases designated as euthyroid (Table 4). The deciding criterion in classifying a patient's postoperative status was the assessment of the clinical picture. Thus a patient with thyroid functional indices in the lower normal[2] range (Cases 6 and 8) or even slightly below (Cases 5 and 7) was designated as euthyroid if, without medication, he was symptom-free and showed no clinical stigmata of hypothyroidism. From the point of view of the success of surgical therapy (with which we are concerned) the results in these patients were very satisfactory.

It should be emphasized that the foregoing criteria are not to be considered as rigid standards, but rather as quantitative guides. In spite of their flexibility, however, there are certain practical inferences. These data suggest, for example, that estimates of the desirable size of the thyroid remnant in the past have been too generous. To what extent the usual conventional standards, shown by the present study to be excessive, have contributed to the incidence of recurrent hyperthyroidism cannot be stated. It is a physiologically sound assumption that remnants weighing over 2 grams probably have contributed to a perceptible degree. Obviously, the question of whether the more radical surgical procedure will result in a lesser incidence of persistent or recurrent goiter will be answered only after much longer periods of observation of the cases in this and similar series. It may be significant that in some of our cases vigorous functional growth of the remnant was still in progress when the studies were brought to a halt.

Thyroidectomies that leave only 800 to 1,000 mg. of parenchyma cannot be performed with safety unless they involve a careful anatomic dissection of the gland, a gentle but sure definition of the recurrent laryngeal nerve, and the demonstration of at least one parathyroid body on each sisde.

SUMMARY AND CONCLUSIONS

The optimum amount of thyroid parenchyma to be left *in situ* when thyroidectomy is performed for nonmalignant disease would, by definition, be the amount that will assure postoperative euthyroidism and reduce to a minimum the likelihood of recurrence. In practice, this is the smallest quantity compatible with a euthyroid state. A knowledge of this amount is of obvious importance, and hitherto it has been estimated largely by

[2] The normal range of values = BMR, −20 to +20 per cent; serum PBI, 3.5 to 7.5 gamma per 100 ml.; and serum cholesterol, 140 to 280 mg. per 100 ml.

empirical guessing. Hence, during a period of two years, we have attempted to measure it quantitatively by studying the postoperative functional state of thyroid remnants in a series of 25 cases of subtotal thyroidectomy performed in comparable groups of diffuse hyperplastic, toxic nodular and nontoxic nodular goiter.

The extent of the operation was controlled by careful measurement of the tissue remnant by a matched-weight method. Postoperatively, all replacement medication was withheld, and at intervals of three to six months tracer doses of radioiodine (I^{131}) were administered. The uptake of the isotope in the thyroid area and, in some cases, its excretion in the urine were determined as primary indices of the functional capacity of the remaining thyroid parenchyma. The relationship between the functional capacity of the thyroid remnant and other laboratory indices of thyroid activity such as the basal metabolic rate and the level of serum protein-bound iodine and cholesterol was also studied.

The tissue remnant showed functional growth in most instances, the only exceptions being tissue rests of exceedingly small size (less than 150 mg.) or of hypoplastic histologic structure. The minimal amount of thyroid tissue to be spared for the maintenance of euthyroidism was found to be much less than hitherto assumed, namely, about 0.8 Gm. in diffuse hyperplastic goiter, and about 1.0 Gm. in toxic nodular goiter.

Observations over several more years are necessary in order to determine whether operations designed to spare only these small amounts of thyroid parenchyma will be followed by a significantly lower incidence of recurrent goiter. The very small size of the optimal thyroid remnant places new emphasis on the need for an anatomic thyroidectomy. Such small pieces of parenchyma cannot be safely dissected out without complete topographic definition of the thyroid gland and careful identification of the recurrent laryngeal nerve and parathyroid bodies.

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RESULTS OF CONSERVATIVE OPERATIONS FOR MALIGNANT TUMORS OF THE THYROID*

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ALL malignant tumors of the thyroid seen on the Surgical Service of the first author between the years 1937 and 1954 have been reviewed. Of 182 such tumors, 59 per cent were classified as papillary carcinoma (Table 1).

PAPILLARY CARCINOMA

About a third (33) of the 107 patients with papillary carcinoma of the thyroid had had a previous operation on the thyroid and will be referred

TABLE 1. INCIDENCE OF TYPES OF MALIGNANT TUMORS OF THE THYROID

	No. of cases	Per cent
Papillary carcinoma*	107	58.8
Encapsulated angioinvasive carcinoma	8	4.4
Medullary carcinoma	7	3.9
Adenocarcinoma	15	8.3
Undifferentiated carcinoma	28	15.4
Squamous-cell carcinoma	1	0.5
Lymphosarcoma	1	0.5
Reticulum-cell sarcoma	4	2.2
Fibrosarcoma	2	1.1
Hodgkin's granuloma of the thyroid	1	0.5
Hodgkin's sarcoma	2	1.1
Secondary neoplasm	6	3.3
Total	*182*	*100.0*

* Including 3 cases of sclerosing microcarcinoma.

to as the *secondary group*. The larger remaining group of 74 patients had had no previous operation on the thyroid itself and will be referred to as the *primary group*. Included in this *primary* group are 23 patients who had had previous neck dissections or biopsies of cervical nodes.

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This article will be included in the bound volume of the 1955 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available early in 1956.

Extent of disease

In the *primary group* of 74 patients (no previous operation on the thyroid), 47 (63.5 per cent) had metastases to the regional lymph nodes at the time of operation. Twenty-seven patients (36.5 per cent) had no gross evidence of lymph node metastases. Four patients (5.4 per cent) had distant metastases when first seen. Three of these had pulmonary metastases and 1 had a metastatic lesion in the femur (Table 2).

In the *secondary group* of 33 patients (previous operation on the thyroid), 22 (66.6 per cent) came to us with residual tumor in the thyroid

TABLE 2. PAPILLARY CARCINOMA—EXTENT OF DISEASE FOUND AT OUR OPERATION

	*Primary group** (74 pts.)	*Secondary group*** (33 pts.)	Total group (107 pts.)
Carcinoma in thyroid and cervical lymph node metastases	47 (63.5%)	22 (66.6%)	69 (64.5%)
Carcinoma in thyroid without cervical lymph node metastases	27 (36.5%)	0	27 (25.2%)
Lymph node metastases only. No carcinoma in thyroid	0	11 (33.3%)	11 (10.3%)
Distant metastases	4 (5.4%)	3 (9.1%)	7 (6.5%)

* *Primary group* = no previous operation on the thyroid.
** *Secondary group* = previous operation on the thyroid.

area and involvement of the regional lymph nodes. Eleven patients (33.3 per cent) had involvement of regional lymph nodes without evidence of recurrence in the thyroid area. Three patients (9.1 per cent) had pulmonary metastases when first seen, and 1 of these also had metastases to the skull and spine (Table 2).

Types of operations

In the *primary group* (no previous operation on the thyroid), removal of the primary tumor in the thyroid was associated with removal of lymph nodes in 46 patients (62.2 per cent). Of this group, 28 patients (37.8 per cent) had unilateral removal of lymph nodes and 18 (24.3 per cent) had bilateral removal of nodes. In 27 patients (36.5 per cent) only the primary tumor in the thyroid was removed and no operation on lymph nodes was performed. One patient who had distant metastases had only a biopsy of a cervical lymph node (Table 3A).

In over half of the cases in the *primary group*, the definitive operation

consisted of total lobectomy, with or without removal of lymph nodes. Total thyroidectomy was performed in only 16 per cent of the cases, usually with bilateral removal of lymph node metastases. In the remaining operable cases the primary lesion was removed by partial lobectomy. Data regarding the types of operations in the *primary group* are recorded in Table 3B.

The sternomastoid muscle was removed on only 2 occasions in the *primary group*. The internal jugular vein was sacrificed in 15 patients. Eight of the 12 patients who had total thyroidectomy had transient postoperative tetany and 1 patient had permanent tetany. A recurrent nerve was sacrificed in 14 patients. Temporary tracheostomy was necessary in

TABLE 3A. PAPILLARY CARCINOMA—EXTENT OF OPERATION IN THE *Primary Group*
(no previous operation on thyroid)

	No. of cases	Per cent
Primary tumor and lymph nodes removed	46	62.2
Only primary tumor removed	27	36.5
Biopsy cervical node only	1	1.3
Total	*74*	*100.0*

4 patients; 2 of these were children under 7 years of age in whom the airway was small. Permanent tracheostomy was never necessary and permanent bilateral vocal cord paralysis did not occur.

In the *secondary group* 22 patients had recurrence in the thyroid area. In 19 of these the thyroidal recurrences and the metastases in the cervical lymph nodes (18 unilateral and 1 bilateral) were removed. Eleven patients had only involved lymph nodes removed, as there was no evidence of recurrence in the thyroid area. Two patients with distant metastases had only biopsies of cervical nodes and 1 patient with diffuse local infiltration had a palliative excision of part of the thyroid tumor. The extent of the operations in the *secondary group* is shown in Table 4A.

Total lobectomy with removal of regional lymph nodes was again the most frequent operation (36.4 per cent). Total thyroidectomy with removal of lymph nodes was performed in 5 patients (15.1 per cent). Seven patients (21.2 per cent) had removal of lymph nodes only, as there was no evidence of recurrence in the thyroid area. Four patients (12.1 per cent) had excision of only a solitary cervical node. The types of operations in the *secondary group* are shown in Table 4B.

The sternomastoid muscle was removed in only 2 of the patients in the *secondary group*. The internal jugular vein was sacrificed in 14 patients.

TABLE 3B. PAPILLARY CARCINOMA—TYPES OF OPERATIONS EMPLOYED IN THE *Primary Group*

(no previous operation on the thyroid)

Total thyroidectomy			
without removal of lymph nodes	1		
with unilateral removal of lymph nodes	1		
with bilateral removal of lymph nodes	10		
Total		12	16.2%
Total lobectomy			
(with or without removal of isthmus and part of other lobe)			
without removal of lymph nodes	12		
with unilateral removal of lymph nodes	22		
with bilateral removal of lymph nodes	8		
Total		42	56.8%
Partial lobectomy			
(with or without removal of isthmus)			
without removal of lymph nodes	12		
with unilateral removal of lymph nodes	4		
with bilateral removal of lymph nodes	0		
Total		16	21.7%
Bilateral subtotal thyroidectomy			
without removal of lymph nodes	2		
with unilateral removal of lymph nodes	1		
with bilateral removal of lymph nodes	0		
Total		3	4.0%
Biopsy cervical node only (distant metastases present)			
Total		1	1.3%
Total		*74*	*100.0%*

TABLE 4A. PAPILLARY CARCINOMA—EXTENT OF OPERATION IN THE *Secondary Group*

(previous operation on the thyroid)

	No. of cases	Per cent
Primary tumor and lymph nodes removed	19	57.6
Only lymph nodes removed (no evidence of recurrence in thyroid area)	11	33.3
Biopsy only	2	6.1
Palliative resection of the thyroid	1	3.0
Total	*33*	*100.0*

There were 4 cases of transient and 1 of permanent postoperative tetany. A recurrent nerve was sacrificed in 6 patients; in another 6, unilateral vocal cord paralysis was present preoperatively (previous operation on the thyroid). Tracheostomy was performed in the 1 palliative operation.

TABLE 4B. PAPILLARY CARCINOMA—TYPES OF OPERATIONS EMPLOYED IN THE *Secondary Group*
(previous operation on the thyroid)

Total thyroidectomy			
without removal of lymph nodes	0		
with unilateral removal of lymph nodes	2		
with bilateral removal of lymph nodes	3		
Total		5	15.1%
Total lobectomy			
(with or without removal of isthmus and part of other lobe)			
without removal of lymph nodes	0		
with unilateral removal of lymph nodes	9		
with bilateral removal of lymph nodes	3		
Total		12	36.4%
Partial lobectomy			
without removal of lymph nodes	0		
with unilateral removal of lymph nodes	1		
with bilateral removal of lymph nodes	1		
Total		2	6.1%
Unilateral removal of lymph nodes only (no evidence of recurrence in the thyroid area)		6	18.2%
Bilateral removal of lymph nodes only (no evidence of recurrence in the thyroid area)		1	3.0%
Palliative excision of part of thyroid tumor		1	3.0%
Excision of solitary cervical node or mass		4	12.1%
Biopsy only		2	6.1%
	Total	*33*	*100.0%*

Results of treatment of papillary carcinoma

Only 1 of the 74 patients in the *primary group* (no previous operation on the thyroid) died of papillary carcinoma of the thyroid. Perhaps this patient should not be included in the *primary group* because before his operation he had a needle biopsy of the thyroid. One year later there was a recurrence in the skin at the site of the needle biopsy and three years after this he died with metastases to the lung and bone. This sole example of

systemic metastases developing after operation in the *primary group* suggests that the needle biopsy disseminated the tumor. Five other patients in the *primary group* died of causes other than carcinoma of the thyroid, and without evidence of recurrence, from six months to twelve years after operation (average survival 4.2 years). A sixth patient who had only a biopsy of a cervical node because of the presence of distant metastases died of other causes, but with papillary carcinoma still present four and a half years after the biopsy. The average postoperative follow-up period in the remaining 67 cases was four and a half years, and the median follow-up period was four years. Sixty-four patients in this latter group were followed until within the past year. Each of 3 patients at present lost was followed for five years or more postoperatively and each was free of disease when last seen.

Following our first operation, 16 (21.6 per cent) of the patients in the *primary group* had an additional operation for removal of an involved group of cervical nodes. These additional operations were performed from three months to eight years later (average 2.5 years). In none of these was there recurrence in the thyroid area at the site of previous surgery, but 2 patients had contralateral tumors of the thyroid removed. Only 2 patients (less than 3 per cent) had more than one additional operation.

Despite the fact that lymph nodes were not removed prophylactically when they were not grossly involved, in only 1 of the 27 patients who had no evidence of involvement of nodes at our original operation (Table 2) was there subsequent development of recognizable metastases to cervical nodes (one year postoperatively). This recurrence was effectively corrected by removal of the involved group of nodes.

Of the 33 patients in the *secondary group*, 4 patients and possibly 5 died as a result of carcinoma of the thyroid, from one day to six and a half years after operation (average, two and a half years). A sixth patient died of other causes two months postoperatively, without evidence of recurrence at the time of death (Table 5). The average postoperative follow-up period in the remaining 27 cases in the *secondary group* was three years. All of these patients were followed until within the past year.

Following our first operation, 4 (12.1 per cent) of the patients in the *secondary group* had an additional operation for removal of involved lymph nodes. These additional operations were performed from one to four years later (average, two and a half years). None of these 4 patients had recurrence in the thyroid area. Only 1 patient had more than one additional operation.

Table 5 presents a comparison of results of treatment between the *primary group* of 74 patients who had had no previous operation on the thyroid and the *secondary group* of 33 patients who had had previous surgery of the thyroid. The poor results in the *secondary group* cannot be attributed

to a more advanced stage of the disease at the time of the previous operation because none of these patients was considered to have advanced or inoperable carcinoma at that time. This suggests that dissemination by incomplete excision of the primary tumor may have been a factor in the unsatisfactory results.

TABLE 5. COMPARISON OF RESULTS OF TREATMENT OF PAPILLARY CARCINOMA IN *Primary* AND *Secondary Groups*

	*Primary group** (74 pts.)		*Secondary group*** (33 pts.)		Total (107 pts.)	
Living without evidence of carcinoma	61	(82.4%)	23	(69.8%)	84	(78.5%)
Died of other causes, without evidence of recurrence at time of death	5	(6.8%)	1	(3.0%)	6	(5.6%)
Lost to follow-up, without evidence of recurrence when last observed	3	(4.1%)	0		3	(2.9%)
Living with local recurrence	0		1	(3.0%)	1	(0.9%)
Living with local recurrence and distant metastases	0		1	(3.0%)	1	(0.9%)
Living with distant metastases present preoperatively	3	(4.1%)	1	(3.0%)	4	(3.8%)
Living with distant metastases developing after surgery	0		1	(3.0%)	1	(0.9%)
Died of disease	1†	(1.3%)	4	(12.2%)	5	(4.7%)
Died of unknown cause elsewhere	0		1	(3.0%)	1	(0.9%)
Died of other causes, with distant metastases present (preoperatively and at time of death)	1	(1.3%)	0		1	(0.9%)
Lost to follow-up, with carcinoma still present when last observed	0		0		0	
Total patients	*74*	*100.0%*	*33*	*100.0%*	*107*	*100.0%*

* No previous thyroid operation. Average follow-up, 4.5 years.

** Previous thyroid operation. Average follow-up, 3 years.

† Patient refused operation and had a needle biopsy.

Twenty-two patients from the *secondary group* had incomplete initial operations before coming to us, as indicated by recurrence of the tumor in the remaining thyroid tissue at the site of operation. In addition the 1 patient in the *primary group* who had a needle biopsy should be classified as having had an incomplete initial operation. In 7 (30.4 per cent) of these 23 patients, distant metastases developed (in 3, before coming to us). In 6 patients (including 4 in whom distant metastases developed) further treatment did not eradicate local disease. Four of these patients died of carcinoma.

Among the 81 patients from both the *primary* and *secondary groups*

who had no evidence of recurrence of the primary tumor after the original definitive operation on the thyroid, in only 3 (3.7 per cent) did distant metastases develop (all before coming to us), and none of these 3 has died. The incidence of distant metastases is therefore nearly ten times greater in the group of patients whose thyroid tumors were incised at the time of the first operation.

Five-year end-results in papillary carcinoma of the thyroid

Of the total number of patients (107) in the papillary carcinoma group, including those who had a previous operation on the thyroid and/or cervical nodes, there were 43 upon whom our operation was performed five or more years ago (average over-all postoperative period 9.4 years). In 4

TABLE 6. PAPILLARY CARCINOMA—FIVE-YEAR (OR MORE) END-RESULTS IN THE 39 DETERMINATE CASES FROM BOTH *Primary* AND *Secondary Groups*

	No. of patients	Per cent
Living without evidence of carcinoma	34	87.2
Died of carcinoma	3*	7.6
Living with local recurrence	0	0.0
Living with distant metastases	1**	2.6
Died of other causes, with papillary carcinoma present at time of death	1	2.6
Lost to follow-up, with papillary carcinoma present when last observed	0	0.0
Total	*39*	*100.0*

* Two of these had had previous operations on the thyroid followed by inoperable local recurrences.

** The distant metastases in this case were present preoperatively.

instances the results were indeterminate for evaluation of five-year end-results because the patients died of other causes without evidence of carcinoma before the five-year period was over. However, 1 of these patients died elsewhere in coma and the possibility of cerebral metastases cannot be excluded.

The remaining 39 determinate cases were followed postoperatively from five to seventeen years. Seven patients were followed for over ten years (average 14.7 years) without evidence of recurrence. Table 6 shows the five-year end-results in this determinate group.

OTHER MALIGNANT TUMORS OF THE THYROID

All 8 of the patients with *encapsulated angioinvasive carcinoma* of the thyroid had definitive operations, usually lobectomy. One of these patients had had a previous thyroidectomy. The average postoperative follow-up period was 2.7 years. Six patients were free of disease when last seen and

2 had distant metastases. Of the 8 patients with this type of malignancy, 3 were operated upon five or more years ago and were eligible for determination of five-year end-results. Two of these were followed to the present time without evidence of recurrence; the third was lost to follow-up, but distant metastases were present when the patient was last observed.

There were 7 patients who had *medullary carcinoma* of the thyroid. Three had only biopsy or palliative resection because of the extent of the disease; only 4 had definitive operations, which usually consisted of total lobectomy and neck dissection. One patient had had a previous thyroidectomy. Five of these 7 patients are dead of carcinoma; the median postoperative period of survival was one year. One patient had distant metastases when last seen and 1 is apparently free of disease a little over five years postoperatively. One of the 7 patients survived sixteen years before the development of a fatal recurrence or possibly a new primary tumor. Two of these 7 patients with *medullary carcinoma* were operated on over five years ago and were therefore eligible for determination of five-year end-results. One of them was followed to the present without evidence of recurrence and the other died of carcinoma eight months after a surgical procedure (biopsy).

Seven of the 15 patients with *adenocarcinoma* of the thyroid had had a previous thyroidectomy. Of the 15 patients, 8 were treated by us with definitive operations (usually total lobectomy). Seven patients had palliative resections or only biopsies, because distant metastases were present. The median postoperative follow-up period was one and a half years. Two patients are known to have died of the disease eight months and five years postoperatively, respectively. Ten patients had distant metastases or remaining local disease when last observed and 3 were apparently free of disease. Of the 15 patients in this category, 4 were operated upon five or more years ago. Two of these died of carcinoma within the five-year period and 2 were followed five or more years without evidence of recurrence.

Of the 28 patients with *undifferentiated carcinoma* of the thyroid, 7 had definitive operations, which usually consisted of total lobectomy and neck dissection. The other 21 patients had only biopsies or palliative resections, because of diffuse local infiltration or distant metastases. Thirteen patients are known to be dead of carcinoma, most of them having died within a few months after they were first seen; the other 15 patients were followed only a few months and all had carcinoma when last observed. Eight patients with *undifferentiated carcinoma* were operated upon five or more years ago and were therefore eligible for determination of five-year end-results.

The remaining group of 11 patients with *miscellaneous* types of malignant neoplasms—squamous-cell carcinoma [1], lymphosarcoma [1], reticu-

lum-cell sarcoma [4], Hodgkin's granuloma [1], Hodgkin's sarcoma [2], and fibrosarcoma [2]—had only biopsies or palliative resections, because of diffuse local infiltration or distant metastases. Most of these patients survived only a few months, and none beyond a year.

FIVE-YEAR (OR MORE) END-RESULTS OF TREATMENT IN ALL TYPES OF MALIGNANT TUMORS OF THE THYROID

Of the 182 patients in this total series of malignant tumors of the thyroid, there were 69 upon whom our operation was performed five or more years ago (average postoperative period 9.2 years). In 4 of these the data are not determinate, because the patients died of other causes within the

TABLE 7. MALIGNANT TUMORS OF THE THYROID—FIVE-YEAR (OR MORE) END-RESULTS IN 65 DETERMINATE CASES

	No. of patients	Per cent
Living without evidence of neoplasm	40	61.5
Died of neoplasm	19	29.3
Living with neoplasm present	1	1.5
Died of other causes, with neoplasm present	1	1.5
Lost to follow-up, with neoplasm present	4	6.2
Total	*65*	*100.0*
Total number of failures	25	38.5
Total number of successful results	40	61.5

five-year period. The remaining 65 determinate cases were followed postoperatively from five to sixteen years. The five-year (or more) end-results are shown in Table 7.

SUMMARY

Excellent results may be obtained by conservative operations on most papillary carcinomas of the thyroid and their follicular variants, provided the primary tumor is completely excised and the grossly involved groups of lymph nodes are removed.

The evidence suggests that biopsy or partial excision of papillary carcinoma often disseminates the carcinoma and renders it incurable.

The results of treatment of non-papillary carcinomas of the thyroid are dependent much more upon the type of tumor than upon the type of treatment.

As a result of this survey, it would appear that radical multilating surgery is rarely if ever indicated in the treatment of carcinoma of the thyroid.

THE PATHOLOGIC EVALUATION OF RADICAL NECK DISSECTION FOR CARCINOMA OF THE THYROID GLAND*

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INTRODUCTION

EXTENSIVE surgical procedures in the treatment of cancer are being continually evaluated. This is as true in regard to thyroid cancer as it is in regard to cancer of the breast, stomach, and other viscera. Opinions concerning the advisability of radical neck dissection as a treatment for thyroid carcinoma vary widely, ranging from the belief that it should never be used, to the opinion that it should be carried out in all cases when still surgically feasible, or even extended to include mediastinal dissection.

Unfortunately, the opinions regarding radical neck dissection in treatment of thyroid carcinoma are often based more upon impressions than upon complete evaluation of facts. For this reason, it seemed desirable to review a series of radical neck dissections performed for thyroid cancer over a five-year period by a group of surgeons using similar methods of case selection and similar techniques of dissection. Since this review encompasses a five-year period (1949 through 1953) too recent to allow for complete or adequate follow-up studies, it is hoped that such studies can be reported when all the patients of this series have had the opportunity to survive for five years. The evaluation here is chiefly from an objective pathologic point of view, with no predetermined attempt either to justify or to condemn this particular operative procedure.

During the five-year period, 1949 through 1953, 160 patients with histologically verified thyroid cancer were treated at the Lahey Clinic. Of

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the 160 patients, 68 or 42.5 per cent underwent radical neck dissection. The tissue removed at biopsy or resection was reviewed in each instance.

PATIENTS NOT HAVING RADICAL NECK DISSECTION

The indications for selection of cases for radical neck dissection were reasonably uniform (1). As a rule, all patients with follicular or papillary carcinoma underwent radical neck dissection. There were five groups of cases in which radical neck dissection was not performed (Table 1): (a) In 30 of the 160 patients radical dissection was not carried out because the tumor was extremely small or appeared essentially as a benign adenoma,

TABLE 1. DISPOSITION OF 160 CONSECUTIVE CASES OF CANCER OF THYROID

Radical neck dissection performed		68
Radical neck dissection *not* performed		92
a. Minimal cancer	30	
b. Highly malignant tumor	15	
c. Poor physical condition	11	
d. Local extension	27	
e. Distant metastases	9	
Total		160

except for minimal capsular, lymphatic, or blood-vessel invasion on microscopic examination. Such cancers have been termed "low-grade," "localized carcinoma in adenoma," or "adenoma with invasion." The malignant nature of such tumors cannot be recognized clinically or from gross inspection. (b) In 15 patients radical neck dissection was not performed because of the pathologic diagnosis of highly malignant cancer (carcinoma simplex). Although 6 patients with the diagnosis of carcinoma simplex did undergo radical neck dissection, there was a tendency (particularly among the cases seen during the latter part of this five-year period) to omit this procedure because of the impression that the poor operative results and poor survival rates associated with such highly malignant lesions did not justify the operation. (c) In 11 patients radical neck dissection was omitted because of poor physical condition, such as cardiac difficulty, hypertension and old age. (d) In 27 patients the procedure was not carried out because the tumor had extended so widely in the neck that the operation was not considered feasible. (e) In 9 patients radical neck dissection was not used because of distant metastases to bone, lung, or brain. It will be noted (Table 2) that both distant metastases and extensive local invasion including at times involvement of trachea and esophagus, may occur in *any* type of thyroid cancer.

TABLE 2. DISTRIBUTION OF CASES IN WHICH RADICAL NECK DISSECTION WAS NOT PERFORMED BECAUSE OF TUMOR SPREAD

	Follicular carcinoma	Papillary carcinoma	Simplex carcinoma	Total
Distant metastases	4	2	3	9
Local extension	7	13	7	27

PATIENTS HAVING RADICAL NECK DISSECTION

The 68 cases of thyroid cancer in which radical neck dissection was performed represented predominantly follicular and papillary carcinomas of the thyroid, which were histologically verified and classified prior to the radical operation, often by frozen-section examination. It should be emphasized that the procedure was carried out whether or not cervical lymph nodes were palpable. The surgical technique on which the dissections were based has been reported by Lahey (2).

Pathologic analysis of the 68 cases is presented in Table 3. In 44 (65 per cent) there was involvement of one or more lymph nodes, and in 22

TABLE 3. LYMPH-NODE INVOLVEMENT AND BLOOD-VESSEL INVASION IN 68 CASES OF RADICAL NECK DISSECTION

	Follicular carcinoma	Papillary carcinoma	Simplex carcinoma	Total
Lymph-node involvement				
None	10	13	1	24
1–4 nodes	6	9	3	18
5–9 nodes	4	10	2	16
10 or more nodes	3	7	0	10
Blood-vessel invasion	8	10	4	22

(32 per cent) the tumor showed microscopic blood-vessel invasion. Neither lymph-node involvement nor blood-vessel invasion showed significant variation in incidence according to tumor type, nor was total number of lymph nodes involved in individual cases apparently related to tumor type.

There was no correlation between the extent of lymph-node involvement and the presence of blood-vessel invasion by the cancer (Table 4).

Also investigated was the relationship, if any, between the duration of the thyroid enlargement prior to operation and the number of lymph nodes involved (Table 5). The great majority of patients gave a history of a thyroid "lump" or "mass." These lumps were often present for many years prior to operation, although at times there was a history of recent growth. No relationship between duration of thyroid enlargement and extent of lymph-node metastases was apparent.

TABLE 4. RELATIONSHIP BETWEEN LYMPH-NODE INVOLVEMENT AND BLOOD-VESSEL INVASION

Lymph-node involvement	*Blood-vessel invasion*
None (24 cases)	7 cases
1–4 nodes (18 cases)	7 cases
5–9 nodes (16 cases)	5 cases
10 or more nodes (10 cases)	3 cases

COMMENT

One of the basic aims of this study was to determine a method of predicting from initial tumor tissue examination whether or not lymph nodes might be involved in any individual case. This is an important problem in the pathologic evaluation of cancer at any site. From an analysis of the pathologic data on these 68 cases of thyroid carcinoma in which radical neck dissection was performed, it seems that there is no consistently reliable factor on which the pathologist can base such a prediction. Metastases were found as frequently in papillary as in follicular cancers, and there was no demonstrable relationship between blood-vessel invasion and lymph-node metatases. Furthermore, knowledge as to the duration of thyroid enlargement prior to surgery does not assist in deciding whether or not cervical lymph nodes contain metastases.

A second point worthy of comment is the high incidence of spread of thyroid cancer, either by metastasis or local invasion, at the time definitive surgery is considered. Of 68 cases selected as operable, 44 showed lymph-node metastases at operation; in the cases considered inoperable, 27 showed extensive local spread and 9, distant metastases. These cases constitute 80 of the total 160. Thus, at least 50 per cent of thyroid cancers in this series had metastasized or showed extensive local invasion by the time of operation.

This study obviously does not provide an answer to the problem of the desirability or inadvisability of radical neck dissection as a treatment for thyroid cancer. This problem can be answered only by careful follow-up

TABLE 5. RELATIONSHIP BETWEEN LYMPH-NODE INVOLVEMENT AND DURATION OF THYROID ENLARGEMENT

No. of lymph nodes involved	Duration of thyroid enlargement			
	Less than 1 yr.	1–5 yrs.	Over 5 yrs.	Unknown
None	4	6	4	8
1–4	8	3	5	2
5–9	7	6	2	1
10 or more	2	2	5	1

studies of well documented cases. However, radical neck dissection, as performed in this series, removed considerable cancer in lymph nodes. In instances in which only a few lymph nodes contained metastases, it may be that the procedure was truly a curative one. Warren and Tompkins (3) showed a definite relationship between the extent of lymph-node involvement and cure rate following radical axillary dissection for cancer of the breast. The ultimate fate of radical neck dissection for thyroid cancer must rest upon the results of complete and careful follow-up studies rather than upon opinions or wishful thinking. It is hoped that this report may be preliminary to a detailed follow-up study on the same series of cases.

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CHILDHOOD THYROID CARCINOMA: PATHOLOGIC CONSIDERATIONS AND THEIR THERAPEUTIC IMPLICATIONS*

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DURING the past five years, 79 new patients with carcinoma of the thyroid gland have been seen at the University of Iowa Hospitals. The mean age was 46.7 years; the median, 48 years. Eight or 10.1 per cent were less than 15 years of age. In Table 1 the number of patients in each decade has been indicated. These data agree with the findings of others

TABLE 1

Age (yrs.)	Patients
0–10	5
11–20	8
21–30	12
31–40	7
41–50	9
51–60	10
61–70	15
71–80	7
81–90	6
Total	*79*

(1) and serve to point out that this lesion has an age incidence quite different from that of other malignant neoplasms.

A considerable difference of opinion exists with regard to the proper treatment of patients with carcinoma of the thyroid in all age groups. The slow progression of the lesion with late metastases, seen in all histologic types except the undifferentiated ones, and the lack of histologic uniformity in any one patient are perhaps the two most important factors leading to these differences of opinion.

* Presented at the Annual Meeting of the American Goiter Association, Oklahoma City, Okla., April 28–30, 1955.

This article will be included in the bound volume of the 1955 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available early in 1956.

Eight children with carcinoma of the thyroid provided an opportunity to study at first hand the clinical behavior and natural history of this disorder during childhood. Detailed microscopic studies will be reported and discussed with respect to the possible relationships to management and the clinical course of these patients. A personal follow-up by the author in each case supplemented the data obtained by review of the patient's hospital records. Unusual clinical and pathologic features prompted the previous report of Case 5 (2).

CLINICAL FEATURES

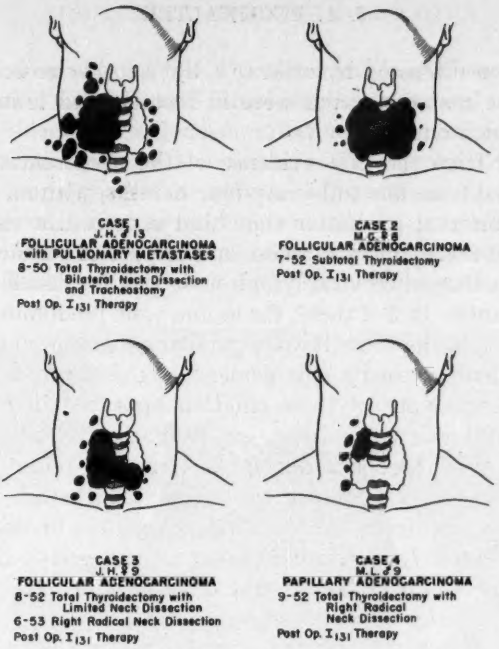
In Table 2 and Figures 1 and 2 are recorded the pertinent clinical data. There were 4 boys and 4 girls. The age of the patients at the apparent on-

TABLE 2

Patient				Interval before treatment	Site of presenting lesion	Follow-up
Case No.	Initials	Sex	Age at onset (yrs.)			
1.	JH	M	11	15 mos.	Node	Cancer-free 5 yrs.
2.	MG	F	8	3 mos.	Thyroid	Cancer-free 2 yrs. 10 mos.
3.	JH	F	8	10 mos.	Node	Cancer-free 2 yrs. 9 mos.
4.	ML	M	9	1 mo.	Node	Cancer-free 2 yrs. 8 mos.
5.	SF	M	7	4 mos.	Thyroid	Dead of neoplasm 7 mos.
6.	SH	F	12	24 mos.	Thyroid	Cancer-free 2 yrs.
7.	DG	F	9	1 mo.	Thyroid	Cancer-free 8 mos.
8.	DH	M	14	1 mo.	Thyroid	Cancer-free 2 mos.

set of the disorder ranged from 7 to 14 years. Fourteen years was arbitrarily chosen as the upper age limit of childhood.

External irradiation had been administered to Patients 4, 5 and 7 during infancy for treatment of an enlarged thymus. Two siblings of Patient 7 died during infancy allegedly because of an enlarged thymus; each had received irradiation treatment. The possible importance of this factor as a cause of carcinoma of the thyroid is at the present a matter for specula-



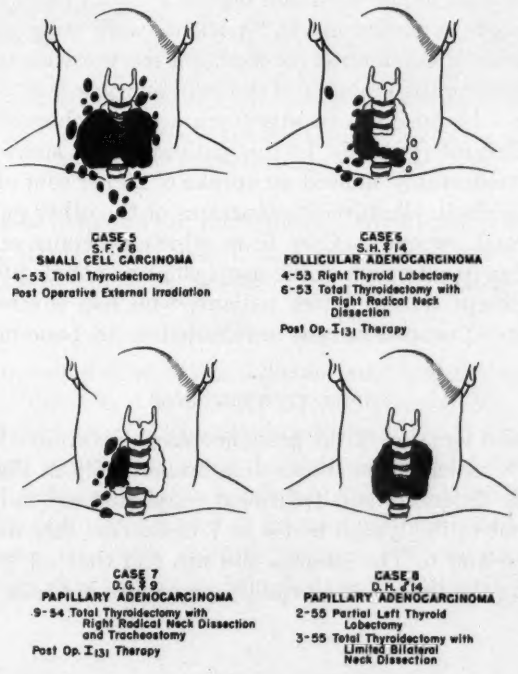
CASE 1
J. H. ♂ 13
FOLLICULAR ADENOCARCINOMA
with PULMONARY METASTASES
8-50 Total Thyroidectomy with
Bilateral Neck Dissection
and Tracheostomy
Post Op. I_{131} Therapy

CASE 2
M. C. ♀ 8
FOLLICULAR ADENOCARCINOMA
7-52 Subtotal Thyroidectomy
Post Op. I_{131} Therapy

CASE 3
J. H. ♀ 9
FOLLICULAR ADENOCARCINOMA
8-52 Total Thyroidectomy with
Limited Neck Dissection
6-53 Right Radical Neck Dissection
Post Op. I_{131} Therapy

CASE 4
M. L. ♂ 9
PAPILLARY ADENOCARCINOMA
9-52 Total Thyroidectomy with
Right Radical
Neck Dissection
Post Op. I_{131} Therapy

FIGURE 1



CASE 5
S. F. ♂ 8
SMALL CELL CARCINOMA
4-53 Total Thyroidectomy
Post Operative External Irradiation

CASE 6
S. H. ♀ 14
FOLLICULAR ADENOCARCINOMA
4-53 Right Thyroid Lobectomy
6-53 Total Thyroidectomy with
Right Radical Neck
Dissection
Post Op. I_{131} Therapy

CASE 7
D. G. ♀ 9
PAPILLARY ADENOCARCINOMA
9-54 Total Thyroidectomy with
Right Radical Neck Dissection
and Tracheostomy
Post Op. I_{131} Therapy

CASE 8
D. H. ♂ 14
PAPILLARY ADENOCARCINOMA
2-55 Partial Left Thyroid
Lobectomy
3-55 Total Thyroidectomy with
Limited Bilateral
Neck Dissection

FIGURE 2

tion, as has been discussed by others (1, 3). Another most unlikely possibility, that the masses treated were in fact thyroid lesions, cannot be categorically ruled out.

The interval from the first evidence of the neoplasm until definitive treatment varied from one to twenty-four months, with an average of 7.4 months. This interval is shorter than that reported in earlier cases (4) and suggests an increasing awareness on the part of physicians regarding this lesion. An enlarged cervical lymph node was the first clinical manifestation in 3 instances. In 2 of these, the lesions were predominantly follicular adenocarcinoma; in the other it was a papillary adenocarcinoma. In the remaining 5 patients primary enlargement of the thyroid gland was the presenting finding. None of these children appeared ill at the time definitive treatment was carried out, except Patient 5, who was seen less than a month prior to death during the terminal phase of the rapidly progressing course of a small-cell carcinoma. General physical examination revealed no significant abnormalities except the findings in the neck. In Patients 4, 6 and 7, several competent examiners failed to detect any palpable nodes. At operation several days later, extensive invasion of multiple cervical nodes by neoplasm was noted.

A euthyroid state was suggested in each case by the results of thyroid function studies which included determinations of thyroidal I^{131} uptake, serum protein-bound iodine level and basal metabolic rate. The preoperative I^{131} body surveys carried out in 6 patients were of no value in establishing a diagnosis of carcinoma, determining the presence of lymph-node spread, or confirming the presence of the pulmonary spread which was suspected in Case 1 because the roentgenogram of the chest showed diffuse pulmonary infiltrates (Fig. 10). In this patient an I^{131} survey undertaken after total thyroidectomy showed an uptake of 20 per cent of the administered dose in the chest. Chest roentgenograms of the other patients showed nothing abnormal, except in Case 5, in which widening of the superior mediastinum due to extension of the neoplasm was noted. Blood and urine were normal except in this latter patient, who had severe anemia and thrombocytopenia; neoplastic cells were noted in the bone-marrow smears (2).

OPERATIVE FINDINGS

The extent and location of the gross neoplasm determined at operation in each of the 8 patients, are shown diagrammatically in Figures 1 and 2; the microscopic diagnosis and treatment employed are indicated. There was involvement of the lymph nodes in 7 instances; this was bilateral in Cases 1, 2, 3, 5 and 6. The surgeon did not feel that all gross neoplasm was removed at the time of the primary procedure in Cases 1, 2, 5 and 6.

Direct invasion of the trachea was noted in Case 1, and there was also extensive thyroid and bilateral lymphnode involvement (Fig. 3). In Case 2 partial thyroidectomy with decompression of the trachea was performed in the presence of nonremovable neoplasm. The parents subsequently refused further surgery. An invasive neoplasm which had extended into soft tissues throughout the neck precluded the possibility of complete extirpation in Case 5. At the time of total thyroidectomy and unilateral radical neck dissection in Case 6, grossly involved nodes on the contra-

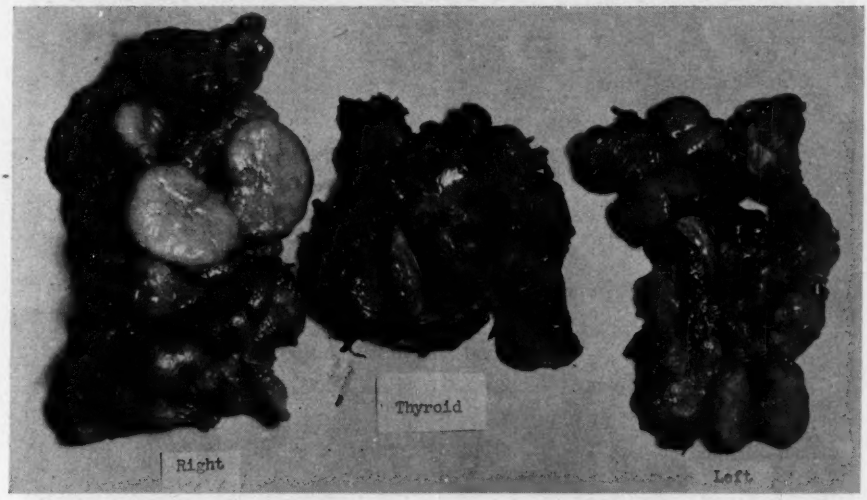


FIG. 3. *Case 1.* Gross specimens showing extensive neoplastic invasion of the thyroid and bilateral groups of cervical nodes.

lateral side were palpated but not removed. Involvement of the prethyroid muscles was observed in Cases 1, 2, 3 and 5. In Cases 3, 4, 7 and 8 no gross neoplasm remained at the end of the definitive surgical procedure.

MICROSCOPIC PATHOLOGY

The microscopic diagnosis was follicular adenocarcinoma in 4 instances, papillary carcinoma in 3 and small-cell carcinoma in the remaining case. The sound classification of these lesions proposed by Warren has been used (5). Follicular or papillary refers to the predominant histologic pattern and does not necessarily exclude other histologic patterns. In Cases 3, 5, 7 and 8 many sections obtained of the primary lesion and invaded lymph nodes showed a relatively uniform pattern—for example the similarity between the primary growth and the node metastasis in Case 3 (Fig. 4).

In Case 1 the lesion was predominantly a follicular adenocarcinoma. However, a section obtained from the thyroid gland showed a follicular and papillary pattern in one field (Fig. 5A). The predominant pattern in the lymph nodes was that of a well differentiated colloid-forming follicular adenocarcinoma (Fig. 5B). Multiple sections of the primary thyroid lesion

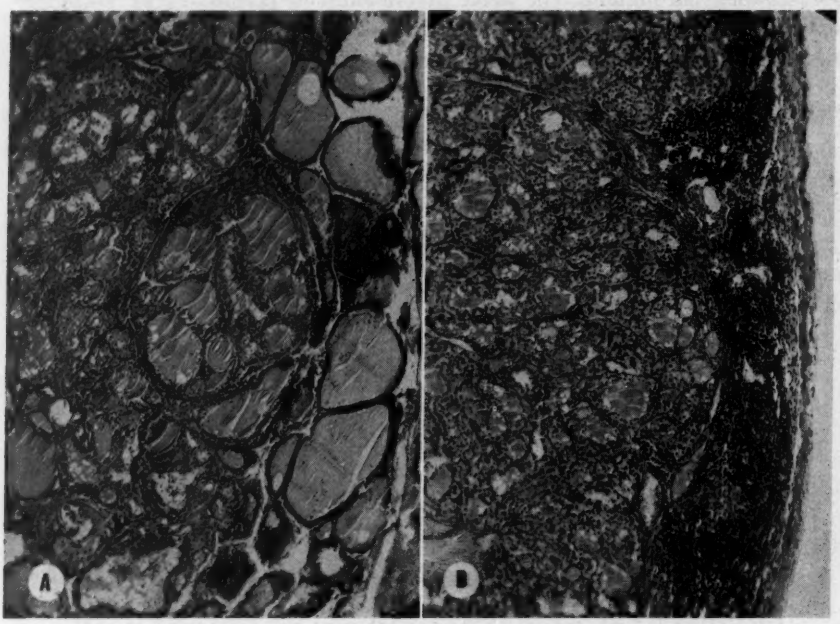


FIG. 4. **A.** *Case 3.* Section from the primary lesion in the thyroid gland showing follicular adenocarcinoma and normal thyroid tissue.

B. Section of a lymph node invaded by well differentiated colloid-forming follicular adenocarcinoma.

in Case 2 showed a similarly well differentiated follicular adenocarcinoma (Fig. 6A), whereas the neoplasm manifested a papillary form in some of the lymph node sections (Fig. 6B). In Case 4 (Fig. 7)—a predominantly papillary lesion—both follicular and papillary areas were noted in the various involved nodes. Follicular and papillary areas were observed in the primary and secondary lesions of Case 6 (Fig. 8).

TREATMENT

There was no uniform method of management of these patients. This is largely because 6 of the patients were referred to the University Hospitals for study and further treatment after the diagnosis has been established

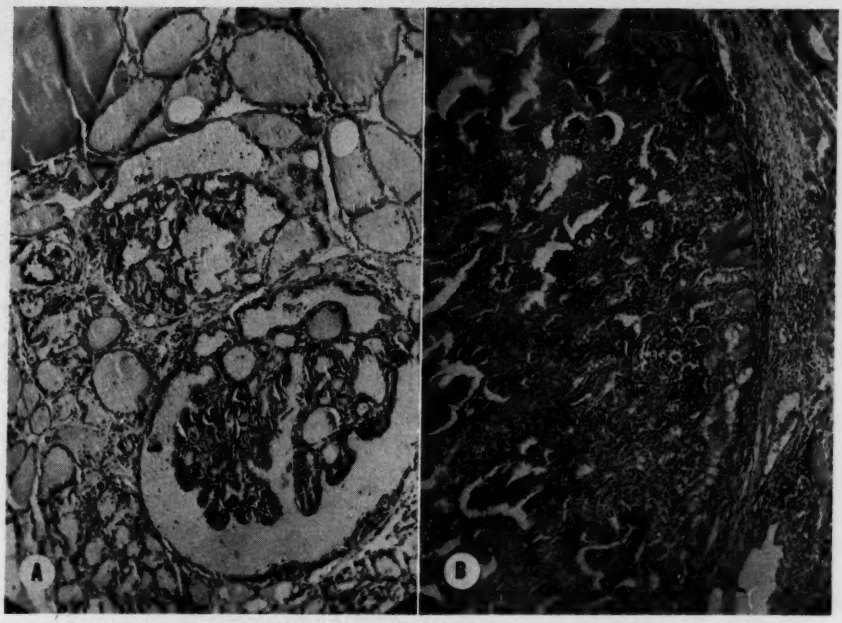


FIG. 5. **A.** *Case 1.* Section from the thyroid gland showing adenocarcinoma with both papillary and follicular pattern.

B. Section from an involved lymph node showing a well differentiated colloid-forming follicular adenocarcinoma.

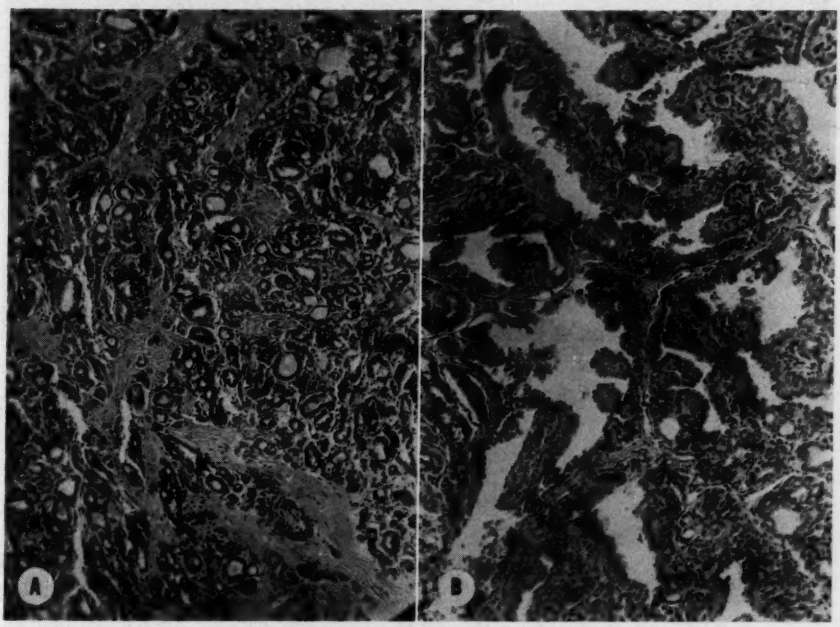


FIG. 6. **A.** *Case 2.* Section from the thyroid showing follicular adenocarcinoma.

B. Section from an involved lymph node showing the pattern of papillary adenocarcinoma.

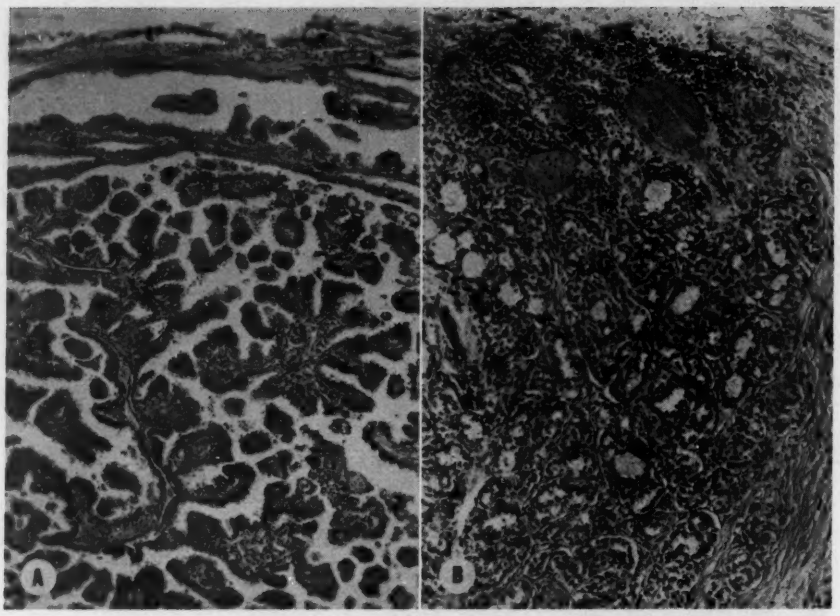


FIG. 7. **A.** *Case 4.* Lymph-node metastasis showing the pattern of a papillary adenocarcinoma.

B. Lymph-node metastasis showing the pattern of a follicular adenocarcinoma.

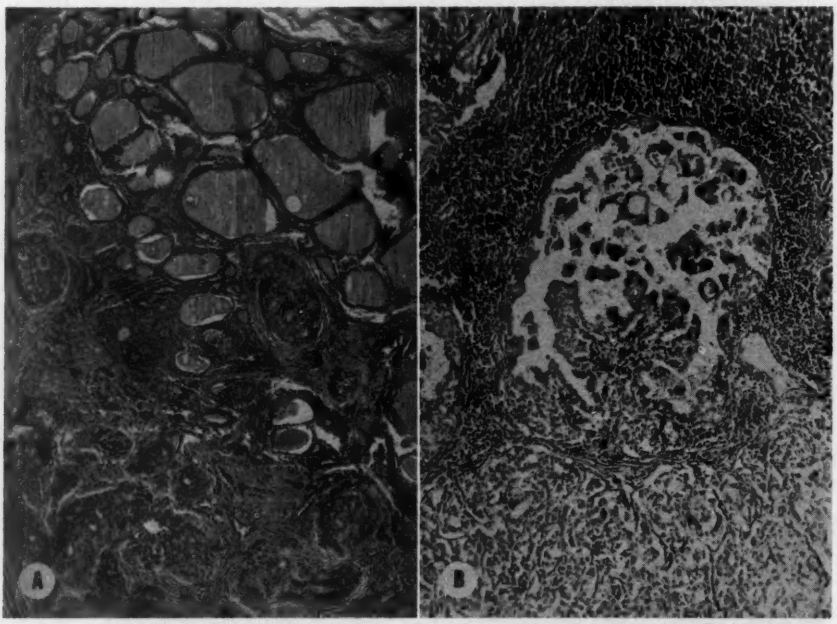


FIG. 8. **A.** *Case 6.* Section from thyroid showing normal tissue and follicular adenocarcinoma.

B. Section of an involved lymph node showing papillary, follicular and relatively poorly differentiated neoplasm.

and after partial treatment had been accomplished. Furthermore, among the surgeons responsible for their care at the University Hospitals, complete agreement in regard to the proper treatment of this lesion has not existed. This situation resulted in some variation in the management of the individual cases, which provided an additional advantage in following the biologic behavior of the lesions and their response to treatment.

In general, the primary treatment was complete surgical extirpation of all the gross neoplasm. Except in 2 instances in which the diagnosis was established by a preliminary biopsy of an involved node, the definitive surgical procedure was carried out at the time the diagnosis was made. The 15 different operations upon these patients included biopsy, and hemi-, subtotal or total thyroidectomy, with or without various types of neck dissection. Tracheostomy was performed at the time of definitive surgery in 3 patients. It is the author's experience that this is rarely necessary and should be undertaken only when there is definite evidence of upper respiratory obstruction.

Postoperative morbidity was low and there was no mortality. In Patients 3 and 7, hypoparathyroidism developed postoperatively and has persisted to date. Unless the lesion extends posteriorly, it is unnecessary and undesirable to remove the posterior false capsule of the thyroid, in juxtaposition to which most often lie the parathyroids. All of the patients became myxedematous two to four months following total thyroidectomy (or ablation of remaining thyroid tissue by I^{131} in Case 2). Satisfactory control was obtained by the administration of 120 to 240 mg. of desiccated thyroid daily. No aberration in the development of these children was noted following total thyroidectomy. The parents were unable to detect changes in behavior, attitudes toward work, or progress in the home and school when the child was taking the proper amount of thyroid. Following radical neck dissection there was minimal disfigurement and disability (Fig. 9). One would not seem justified in compromising the adequacy of the operation by saving the sternocleidomastoid muscle as has been advocated (6), or otherwise limiting the procedure.

Radioactive iodine was the most important form of adjunctive therapy. Radioautographs which were made in 6 cases at the time of definitive surgery were of little value in predicting the possible effectiveness of subsequent therapy. In anticipation of the subsequent use of I^{131} in treating residual or recurrent neoplasm, total thyroidectomy was performed in 6 cases. As normal thyroid tissue has greater affinity for I^{131} than does the neoplastic tissue, all normal tissue was removed, since it would otherwise take up the I^{131} subsequently administered. Ablation of the remaining normal thyroid tissue was accomplished with appropriate doses of I^{131} in Case 2.

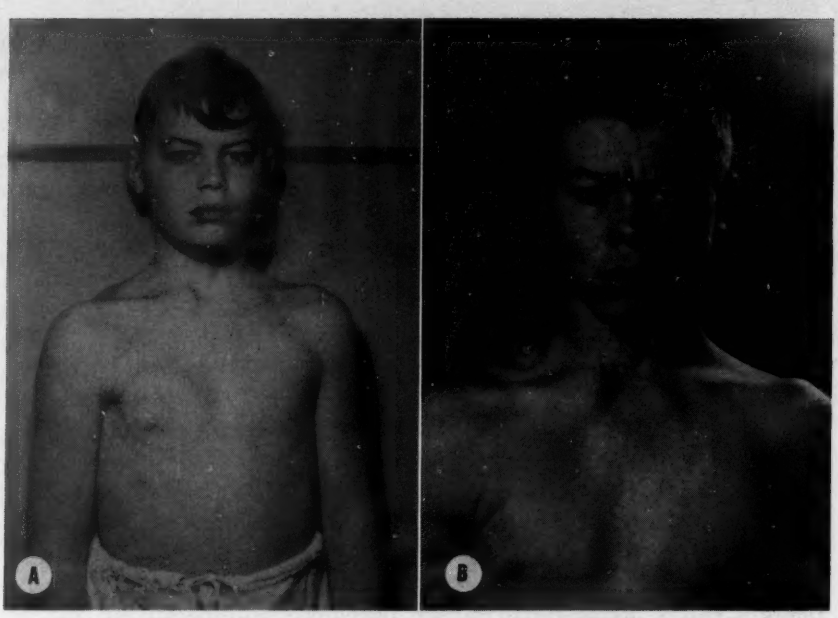


FIG. 9. **A.** *J. H., Case 1.* Before total thyroidectomy and bilateral neck dissection. **B.** Four years after operation.

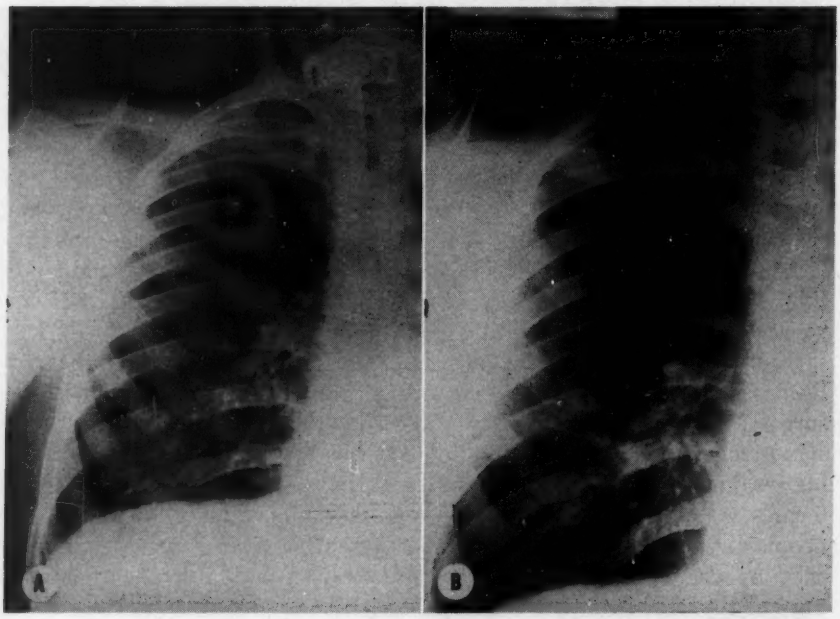


FIG. 10. **A.** *Case 1.* Roentgenogram of the chest showing right pulmonary field infiltrates (after total thyroidectomy and neck dissection before the start of I^{131} therapy). **B.** Four years later, showing the clearing which occurred with I^{131} therapy.

Within the first week following surgery, a survey was made of the thyroidal uptake of radioactive iodine. Therapeutic doses of I^{131} were given to all patients except in Case 5 and Case 8. In the former, the microscopic findings suggested that the lesion would not take up I^{131}; this was confirmed by tracer study. In Case 8 the papillary adenocarcinoma was grossly restricted to the thyroid and therefore completely excised. Subsequent tracer studies showed no uptake. In all the other patients, it was thought that gross neoplasm remained after surgery, or that there was an extensive lesion and lymph-node spread with a good possibility of residual undetected gross neoplasm. Multiple smaller doses of radioiodine were used, rather than a single large dose. With tracer studies as a guide, it was possible to administer with reasonable accuracy the approximate dose required to destroy or control the neoplasm.

The interval between follow-up visits was determined by the response to treatment, as indicated by examination and tracer studies. When the patients became myxedematous, thyroid therapy was started. Since the administration of thyroid blocks the uptake of I^{131} by the thyroid gland or neoplasm, it was discontinued two weeks prior to follow-up visits. At the time of the follow-up visit a physical examination, tracer study and roentgenogram of the chest were obtained. Results of serum protein-bound iodine determinations and basal metabolic rates were non-contributory. In cases in which thyrotropic hormone and propylthiouracil were used, there was no noticeable increase in the thyroidal uptake of I^{131}. Only in Patient 5 was external irradiation employed. Three thousand roentgens in air failed to influence favorably the course of this lesion, which was rapidly progressive and had a fatal issue a little more than seven months from the time enlargement of the neck was first noted (2).

In Table 3 is a summary of the therapy employed and course of the disease in Patient JH (Case 1). This patient had an extensive lesion (Fig. 3) with tracheal invasion and diffuse infiltration of both lung fields (Fig. 10), which was predominantly follicular but showed definite papillary areas (Fig. 5). A striking feature was the uptake of I^{131} detected over the chest after total thyroidectomy, when there had previously been none. Just a few months less than five years from the time of surgery, this patient remains clinically free of neoplasm, and a roentgenogram of the chest has shown clearing of the previously noted infiltrates (Fig. 10B).

Patients 2 and 6, in whom there was thought to be residual neoplasm after operation, were treated similarly, receiving total dosages of 22 mc. and 40 mc. of I^{131}, respectively. Current tracer studies indicate no thyroidal uptake, and physical examination reveals no evidence of persisting neoplasm. Both lesions were predominantly follicular, but papillary areas were noted in each.

When Patient 3 was first seen at the University Hospitals following total thyroidectomy with removal of all gross neoplasm, as much as 50 per cent of the tracer dose of I^{131} was taken up in the neck. This uptake was regarded as highly suggestive of residual neoplasm. In view of the recent extensive surgery which had resulted in hypoparathyroidism and a lesion which histologically was felt to be most favorable for I^{131} therapy, it was elected to treat her with radioactive iodine. During the next month a total of 30 mc. was given; following this the uptake decreased to negligible levels. Ten months from the time radioactive iodine therapy was initiated, several

TABLE 3. COURSE IN PATIENT LH (CASE 1)

Date		I^{131} uptake (% of dose)	I^{131} uptake in	
			Neck	Chest
July 28, 1950		24	++++	0
Aug. 17		20	++++	+ to 0
Aug. 19	Total thyroidectomy; neck dissection			
Sept. 5		20	+	++++
Sept. 11 to 15	I^{131}, 60 mc. (26,355r calc. tumor dose)	35	+	++++
Oct. 31	I^{131}, 20 mc.	16	+ to 0	+++
Dec. 26	Myxedematous	21	+ to 0	++
Dec. 29, 1950	After TSH	12	+ to 0	+
Feb. 21, 1951		0	0	0
Aug. 16, 1951		0	0	0
July 16, 1952	After propylthiouracil; later TSH	4	0	+ to 0
June 8, 1953		3	0	0
June 21, 1954		2	0	0
Jan. 6, 1955		2	0	0

small masses became palpable in the right side of the neck. Results of tracer and survey studies were negative at this time. When biopsy indicated follicular adenocarcinoma, a right radical neck dissection was performed. In the microscopic sections there was viable neoplastic tissue showing cells with vacuolated cytoplasm, pleomorphic nuclei and considerable desmoplastic reaction, all of which could have been related to the radiation therapy (Fig. 11). In the interval since this operation, results of I^{131} uptake and survey studies have continued negative and the patient remains clinically free of neoplasm.

Small therapeutic doses of I^{131} were given to Patients 4 and 7 in an effort to ablate remnants of thyroid or residual neoplasm, the presence of which

was suggested by a borderline uptake in the neck area following total thyroidectomy. At present, results of tracer and survey studies remain negative and there is no clinical evidence of carcinoma.

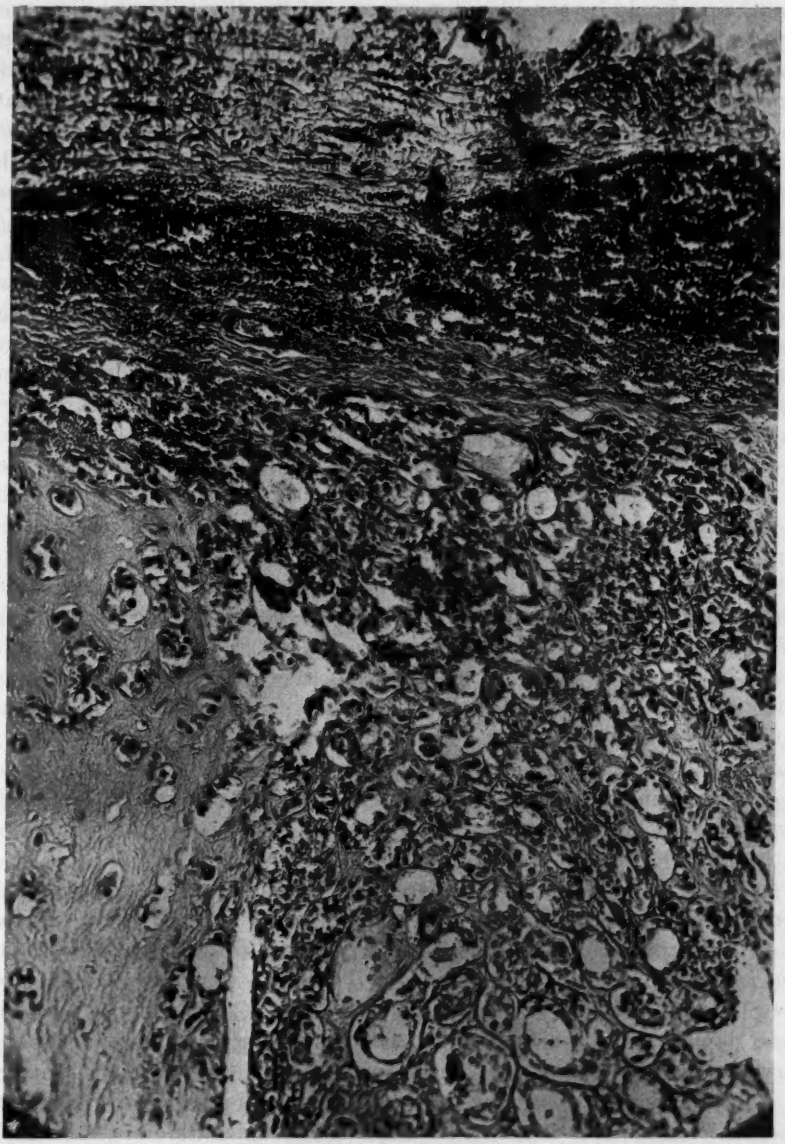


FIG. 11. *Case 3.* Section from lymph node invaded by follicular adenocarinoma ten months after therapeutic dose of I^{131}.

DISCUSSION

The appearance of a non-tender mass in the thyroid gland or the cervical region of a child, unassociated with an upper respiratory infection or an exanthem, should be considered carcinoma of the thyroid until disproved by adequate biopsy. Among the 8 children of this study, definitive therapy was delayed ten months or more in 3 of them because the possible significance of such a mass was not understood. Cases 4, 6 and 7 demonstrate well the limitations of examination of the neck in detecting the presence of involved lymph nodes. It seems probable that the noted increase in the incidence of childhood thyroid carcinoma is largely a function of an increasing awareness and consequent earlier diagnosis of this lesion.

Of first importance is the process of establishing whether the lesion is a differentiated or undifferentiated one. The clinical behavior of these two groups of lesions differs so widely that for practical purposes they may be considered as two distinct unrelated neoplasms that just happen to occur together in the thyroid gland. Constituting the larger number of thyroid carcinomas and occurring more often in the younger age groups, the differentiated lesions are characterized by a prolonged course with late metastases. Conversely, the undifferentiated lesions, which occur more often in the older patients, are characterized by early metastases and a rapidly progressing and usually fatal course. The characteristics and natural history of this group of neoplasms are similar to those of adenocarcinomas of other viscera; there seems to be no prototype of the well differentiated adenocarcinoma of the thyroid. This could account for the different age incidences with regard to thyroid neoplasms referred to in the first paragraph (Table 1). It should be stressed that the exceptions in regard to age [such as SF (Case 5) or the older patient with the papillary lesion] are sufficiently numerous so that a histologic diagnosis must be established in each case, regardless of the age of the patient, before a decision is made regarding definitive therapy. The difference in the natural history of the two groups of lesions is related to the histologic structure of the neoplasm rather than to the age of the patient (7).

It seems probable that all differentiated lesions are adenocarcinomas showing histologic differences which are unimportant in regard to treatment and prognosis. Thus, in Cases 1, 2 and 6 in which the primary lesion was follicular, papillary areas were noted either in the thyroid or invaded lymph nodes. Sections of two lymph nodes from Case 4 revealed well defined papillary and follicular areas, whereas the primary lesion was papillary. In the 3 remaining cases the lesion had a relatively uniform pattern. If it were possible to obtain serial sections from all areas of the neoplasms and their metastases it seems probable that similar differences could be

demonstrated in all well differentiated thyroid carcinomas. It thus becomes apparent why radioautographs were of limited value in predicting the result of I^{131} therapy. Serial-section autographs of the primary neoplasm and all its metastases would be required to make this a practical tool. In contrast, the radioactive iodine uptake has proved to be of great value because it measures the total capacity of the lesion to take up I^{131}.

Surgical extirpation of the well differentiated lesion and its metastases should be considered the primary form of therapy. If ancillary I^{131} therapy is to be considered, total thyroidectomy should be performed, regardless of whether one lobe or the entire thyroid is involved by the neoplasm. If there is cervical node and/or adjacent soft tissue involvement, unilateral radical neck dissection should be part of the definitive procedure. Contralateral neck dissection is later indicated, if there is bilateral node involvement. In the advanced lesion with mediastinal node involvement there would seem to be a place for the thoraco-cervical approach and mediastinal node dissection (8). Although slowly progressing, this lesion is nevertheless a malignant one; it metastasizes and kills. The application of these surgical principles remains the basis for the management of such lesions in children and adults until an equally effective form of therapy is found.

The limitation of effective treatment to local areas and the undesirable side-effects which may accompany external radiation prompted our use of I^{131} therapy. In the 3 cases in which residual tumor was thought to remain after surgery (1 with pulmonary metastases), therapeutic doses of I^{131} eliminated all the uptake and the patients have remained clinically free of disease. Since papillary areas were noted in all these lesions, the apparently continuing satisfactory response was not entirely expected. In Case 3, in which a well differentiated colloid-forming follicular adenocarcinoma was demonstrated, an initially high I^{131} uptake following total thyroidectomy suggested the presence of residual neoplasm. Ten months later, after therapy had reduced the I^{131} uptake to negligible levels, a radical neck dissection was performed, and neoplasm was found in the cervical nodes. This was a lesion which was thought to offer an optimal chance for effective I^{131} therapy.

These cases suggest the present difficulties in predicting the result of treatment of these neoplasms with radioactive iodine. Our experience with such lesions and their affinity for I^{131} is much better than that generally reported. An undetected screening factor acting to select cases may be partly the reason for this discrepancy. Age per se seems an unlikely explanation. Some of the discouraging results of radioiodine therapy may be related to its use in the undifferentiated lesions or the insufficient clinical

trial under the proper circumstances. Continued follow-up over a period of many years will test the validity of these impressions and the reasonableness of this form of management.

SUMMARY

1. The pertinent clinical features exhibited by 8 children with carcinoma of the thyroid have been reported.

2. The gross and microscopic characteristics of the lesions have been illustrated and discussed.

3. Surgical extirpation of all gross neoplasm is recommended as the primary form of treatment of well differentiated adenocarcinoma of the thyroid in children. Radioiodine was used effectively as ancillary therapy in these patients. Its further use seems warranted by the results obtained.

4. The possible therapeutic implications of the pathologic findings have been discussed.

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The Endocrine Society

THE 1956 ANNUAL MEETING

The Thirty-eighth Annual Meeting of The Endocrine Society will be held in the Palmer House, Chicago, June 7, 8 and 9, 1956.

THE 1956 AWARDS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg; 1955—Dr. Jack Gross. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

This Fellowship was established in 1947. It is designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. The Fellowship is awarded on alternate years (1955, 1957, etc.) and the stipend, which will not exceed $5,000, may be

divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of the Endocrine Society; the Ciba Award; and the Ayerst, McKenna and Harrison Fellowship may be made by any member of the Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *November 1* each year.

Proposals for appointments as Scholars of The Endocrine Society should be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *November 1* each year.

The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1.

The American Goiter Association

THE 1956 ANNUAL MEETING

The next Annual Meeting of The American Goiter Association will be held in the Drake Hotel, Chicago, Illinois, May 3, 4 and 5, 1956.

ANNOUNCEMENT OF THE VAN METER PRIZE AWARD FOR 1956

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held at the Drake Hotel, Chicago, Illinois, May 3, 4 and 5, 1956, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany, New York, not later than *January 1, 1956*. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

ANNOUNCEMENT OF THE AWARD OF MERIT

The American Goiter Association Award of Merit and its Honorarium of $1,000.00 is again offered by its anonymous donor for 1956. Brown M. Dobyns, M.D. received this award in 1954 and Alexander Albert, M.D. received it in 1955. Under the terms of the original gift, 1956 is the third and final year this award will be offered.

The terms of the gift specify that this sum shall be given to a member of the Association under 45 years of age who has made the most important contributions to the knowledge, understanding or treatment of thyroid disease.

Candidates for this award are to be nominated by members of the As-

sociation. When making a nomination, complete details of the nominee's present and past positions and training must be submitted. A complete bibliography of the nominee's publications is required. A full explanation of the reasons for nominating the candidate must be given.

The candidates submitted are to be reviewed by an anonymous committee appointed by the President. The chairman of this committee will present the deliberations and decision of said committee to the Executive Council in advance of the annual meeting.

The award is to be called The American Goiter Association Award of Merit and it shall be presented at the annual banquet.

You are requested to send your nominations in duplicate to this Secretary, making certain the information required by the deed of gift is included. All nominations must be received *not later than November 1, 1955.*

JOHN C. MCCLINTOCK, M.D.
Secretary

RECIPIENT OF THE VAN METER PRIZE AWARD FOR 1955

Van Meter Prize

The Van Meter Prize for 1955 was awarded to *Dr. Jacob Robbins* for his essay with *Drs. J. E. Rall* and *Rulon W. Rawson* entitled "A New Serum Iodine Component in Patients With Functional Carcinoma of the Thyroid."

Dr. Robbins was born in Yonkers, New York, September 1, 1922. He received his A.B. degree from Cornell University in 1944 and his M.D. degree from Cornell University Medical College in 1947. His internship was served in the New York Hospital, following which he was a resident in medicine at Memorial Hospital for Cancer and Allied Diseases, New York, from 1948 to 1950. He held a Damon Runyon Clinical Research Fellowship for the three years, 1949 to 1952. From 1951 to 1953 he was clinical assistant in medicine at Memorial Hospital and is now an assistant attending physician. He is currently on leave of absence as a senior assistant surgeon, United States Public Health Service, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

First Honorable Mention

First Honorable Mention was given to the essay by *Drs. Monte A. Greer* and *Leslie J. DeGroot* entitled "A Study of the Effect of Stable Iodide on Thyroid Secretion in Thyrotoxicosis: A Clue to the Pathogenesis of Graves' Disease."

Second Honorable Mention

Second Honorable Mention was given to the essay by *Drs. Marvin E. Levin* and *William H. Daughaday* entitled "The Influence of the Thyroid on Adrenocortical Function."

RECIPIENT OF THE AWARD OF MERIT FOR 1955

At the 1955 Annual Meeting, the American Goiter Association Award of Merit was presented to *Dr. Alexander Albert* of Rochester, Minnesota.

Dr. Albert was born on March 25, 1911 in Spring Valley, New York. He received his B.A. degree at St. Stephens College, New York, in 1932, his M.A. degree at Harvard College in 1933, his Ph.D. degree at the same institution in 1935, and his M.D. degree at Harvard Medical School, Boston, in 1943. His internship was served at Beth Israel Hospital, Boston—in Surgery 1943–1944, and in Medicine 1944–1945. He worked in the Thyroid Clinic of the Massachusetts General Hospital, Boston, 1945–1946. During the year 1946–1947 he was a research associate at the Mayo Clinic, Rochester, Minnesota, becoming a member of the staff in 1947. At present he is a member of the Section of Physiology and Head of the Endocrinology Laboratory at the Mayo Clinic, and Associate Professor in Physiology, The Mayo Foundation.

Dr. Albert has been very active over a period of years in studying the physiology of the thyroid, including his work on exophthalmos, enhancement of the effect of TSH by thiouracil, the entero-hepatic circulation of thyroxine, and the action of triiodothyronine. He well deserves this recognition.

RECIPIENTS OF THE 1955 AWARDS FOR MERITORIOUS SERVICE

At the 1955 Annual Meeting, the American Goiter Association presented certificates for long and meritorious service to:

Dr. V. E. Chesky, Halstead, Kansas
Dr. James Howard Means, Cambridge, Massachusetts